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ADENOMATA OF THE CAROTID GLAND

By Mont R. Reid

(From the Surgical Department of The Johns Hopkins Hospital)

Tumors of the carotid body have been studied by many authors. The recorded cases, however, are scarcely more than the number of authors who have written on the subject. Steindl, in 1915, published a carefully studied case and collected from the literature 41 others. Recently Reenstierna has reported two cases and found in the literature additional ones, bringing the total of reported cases to the number of 66.[1] Most authors have based their report on the observance of one case, 1 author on four cases, 2 on three cases and 3 on two cases.

From Professor Halsted's clinic three cases may be added to the list. Two of these were operated upon by myself; a specimen of the tumor in the remaining case was referred to me for diagnosis at the time I was assistant in the Department of General Pathology.

Case 1.—(Surgical Nos. 31826 and 48031.) A white man, aged 46, was admitted to The Johns Hopkins Hospital March 28, 1913, complaining of a swelling in the left side of his neck. The family history was unimportant. In his past life he had had the usual diseases of childhood, including scarlet fever at the age of eight and typhoid fever at 18.

One morning in February, 1908, he accidentally discovered a small lump about midway between the angle of the jaw and the clavicle. He thought that it had appeared over night. Without causing any discomfort other than that of the disfigurement, the lump gradually grew larger "in spite of all sorts of treatment"—drugs and local applications. Pulsation of the tumor was first observed in 1911 and had become much more pronounced in the two years before his admission. A few weeks before coming to The Johns Hopkins Hospital he was seen in Philadelphia by a surgeon who told him he had an aneurysm and advised him to see Dr. Halsted.

On his first admission to The Johns Hopkins Hospital, March 28, 1913, a diagnosis of carotid aneurysm was made by all of the many surgeons who examined the tumor. A large, expansile, pulsating mass involved the left side of the neck extending from the lobe of the ear to within 3 cm. of the clavicle, and from the middle of the neck anteriorly to the trapezius muscle posteriorly (Fig. 1). Its external circumference was 17 cm. The trachea was displaced 1 cm. to the right of the midline. A thrill was easily felt along the posterior part of the tumor. The mass was slightly compressible. Firm pressure below the tumor did not lessen the pulsation in it. There was a scarlatiniform flush over the upper part of the chest and the neck. There was expansile pulsation over the whole tumor. Careful examination of the eyes and eyelids revealed no evidence of disturbance of function of the cervical sympathetic nerves. Blood pressure 160. Dr. G. J. Heuer wrote: "The left wall of the pharynx is dislocated toward the median line, so that the left tonsil is pushed inward and lies directly in the median line just below the uvula. The entire wall of the pharynx pulsates visibly. The vocal cords can hardly be seen, but from a fleeting view both cords seem to be active." Wassermann, negative.

Operation, April 1, 1913, by Dr. Halsted. Ligation of the common carotid artery. It was observed that the carotid artery occupied a more lateral position than was normal. About it there were numerous dilated venules, suggesting an angioma. These venules bled easily. The artery was dilated and its wall was very soft. The bleeding from the angiomatous tissue made it necessary to

[1] This author excludes a few cases reported as carotid body tumors. Winslow refers to 72 cases; Schley to 76; and Lund to 80. The correctness of the diagnosis in several instances is questionable.

divide the sternomastoid muscle so that the artery could be ligated without lifting it from its bed. The omohyoid and platysma muscles were also divided. After ligation of the artery these muscles were sutured.

At the end of the operation there was no pulsation in the tumor.

April 6, 1913, it was noted that the tumor was much softer and more compressible. No pulsation. Its measurements had decreased 5 cm. A faint bruit, however, was audible. The temporal artery rapidly became much larger and tortuous.

April 21, 1913. Patient discharged. A faint bruit was present in one place. No pulsation. No thrill. The mass was smaller.

April 10, 1919. The patient returned because the tumor in his neck had gradually increased in size. The increase had been forward and laterally, and particularly in the lower part of the tumor. He had observed a return of pulsation soon after leaving the hospital, and this had gradually become more evident. The disfigurement caused by the tumor was his chief worry.

About two weeks after the operation in 1913, the vision of the left eye began to fail and in a period of six months to one year was entirely gone. In May, 1917, his eye was removed, the diagnosis of glaucoma having been made by the surgeon. Vision in the right eye remained good. His voice never became impaired.

When seen by me on April 11, 1919, I came to the conclusion that the condition was not a true arterial aneurysm, but probably an angiomatous tumor or an arterio-venous fistula. A huge swelling (Figs. 2, 3 and 4) involved the left side of the neck from the lobe of the ear and the mastoid process to the midline anteriorly and downward almost to the clavicle. The trachea was displaced 2 cm. to the right of the midline. The circumference of the tumor, vertically, was 15 cm.; transversely, 19.5 cm. The superficial temporal vessels were very prominent and tortuous. The pulse was equally well felt in them. Over the tumor and the upper part of the chest there was a diffuse erythematous flush of the skin. The face was suffused. The color of the entire body, but particularly of the face, suggested an abnormally dark pigmentation of the skin. Over the lower part of the tumor there were large, tortuous veins, suggesting an angiomatous condition. A slight heaving pulsation of the whole tumor was visible. This was better seen than felt, although on palpation the mass seemed to be definitely expansile. A diffuse thrill could be felt over the entire tumor but was most marked anteriorly and laterally. One could hear a continuous bruit with a systolic intensification of an almost musical character. On firm pressure the main mass was only slightly compressible. It was noted that palpation produced paroxysms of coughing. The large vessels running over the swelling could be felt as grooves in it. Many of these vessels were rather large, tortuous arteries. No pulsation in the left common carotid artery could be felt, and firm pressure over the region of this vessel did not affect the pulsation of the supposed aneurysm. Hearing was a little impaired in the left ear. The radial pulse was equal on both sides. Systolic blood-pressure, 134; diastolic, 94.

An examination by Dr. S. J. Crowe revealed a complete paralysis of the left vocal cord. *There was no bulging of the left side of the pharynx.* The tonsils occupied normal positions.

April 15, 1919. Operation by Dr. Mont Reid. The operation required 4 hours and 20 minutes and was unusually difficult on account of the extreme vascularity. Before any tissues could be divided it was necessary to apply clamps, for huge vessels were encountered everywhere. There were numerous vessels as large as the normal jugular vein. The carotid artery, which had been ligated at the first operation, was not recognized during this operation. It was necessary to resect a portion of the vagus nerve and the internal jugular vein. The 11th and 12th nerves ran directly through the tumor and had to be divided. The sterno-mastoid muscle was excised with the tumor.

At the completion of the operation we began to study the specimen which, by the time it was removed, we had thought might be an angioma or angio-sarcoma instead of an aneurysm. On sectioning it we were surprised to see that we were dealing with an extremely vascular tumor, which had a beautiful coloring. The center of the tumor was yellowish-brown, whereas towards the periphery many areas were of an amber color. We were certain that we were dealing with a pigmented tumor. Dr. Halsted immediately suggested that the specimen was a tumor of the carotid body. I did not agree, for the frozen section looked exactly like a case of so-called perithelial angio-sarcoma that we had studied in the Pathological Department in 1914. After a brief study of the literature I learned that I was wrong, and as a result, the interesting case of vascular tumor of 1914 is included as Case 3 in this report.

For 36 hours after the operation the patient caused us some anxiety on account of œdema of the epiglottis which interfered with his breathing. After that his convalescence was uneventful, except for the discomfort caused by the division of the hypoglossal and vagus nerves. His voice was not affected, for the left vocal cord was paralyzed before the operation. He left the hospital May 1, 1919, just 16 days after the operation. At that time (Fig. 5), the tortuous vessels were less prominent and the face and neck were much less suffused.

About one month after this patient left the hospital he was seen by Dr. Halsted who was quite surprised at the change in his appearance. The erythematous flush about the neck and the suffusion of the face were gone, the yellowish tinge had disappeared and the skin had taken on its normal color. The large tortuous temporal vessels were not evident.

The specimen of this case (Fig. 7) weighed 190 grams; measured 8.5 x 6.5 cm. Very large vessels ran through the tumor. The coloring and general appearance of the cross-sections were typical of the numerous descriptions in the literature. On microscopical examination of the sections (Fig. 8) the naked eye diagnosis was confirmed.

Case 2.—(Surgical Nos. 46620 and 48293.) A white woman, aged 37, was admitted to The Johns Hopkins Hospital April 30, 1919, complaining of a lump in the left side of her neck. It had been present for four years and had grown gradually in size. When first observed it was very small, and her attention was directed to it by a stinging pain inside the throat. This occasional pain with sometimes a throbbing in the swelling was the only discomfort caused by the tumor. On her first admission to this hospital, October 5, 1918, a diagnosis of lympho-sarcoma was made and she was referred to Dr. Curtis F. Burnam for radium treatment. Numerous treatments failed to have any appreciable effect on the tumor. February 3, 1919, Dr. S. J. Crowe removed a small neighboring lymph gland for diagnosis. The pathological report was a round-cell sarcoma. Other treatments with radium were given but the swelling remained the same size.

The tumor extended from the lobe of the ear and the mastoid process to the middle of the sterno-mastoid muscle and anteriorly to a point midway between the angle and the symphysis of the mandible. The scar caused by the excision of the gland for diagnosis had not become attached to the tumor. The skin over the tumor was freely movable. The mastoid muscle was made taut by the tumor pushing it directly outward. There was a slight tendency to nodular formation in the anterior part of the growth. Upward it seemed to blend with the parotid gland. The tumor was doughy and gave almost the sensation of pitting on pressure. The trachea was in the midline. The tumor was slightly movable laterally but not vertically. It did not move on swallowing. Slight palpation of it provoked paroxysms of coughing.

The common carotid artery was displaced by the growth so that its bifurcation could be seen and felt on the antero-lateral aspect

FIG. 1.—Case 1. March, 1913. Before first operation. Sterno-mastoid muscle compressing the external growth, so that it is causing a conspicuous bulging of the pharyngeal wall.

FIG. 2.—Case 1, as it appeared in 1919. Duration of tumor 11 years. Six years previously the carotid artery was ligated and the sterno-mastoid muscle cut, thus effecting a decompression which permitted a lateral dislocation of the growth. Note the pigmentation of the face and neck, and the prominence of the temporal blood vessels. There was no bulging of the pharyngeal wall.

FIG. 3.—Case 1. Side view, 1919. Note the large blood vessels.

FIG. 4.—Case 1. Posterior view, 1919.

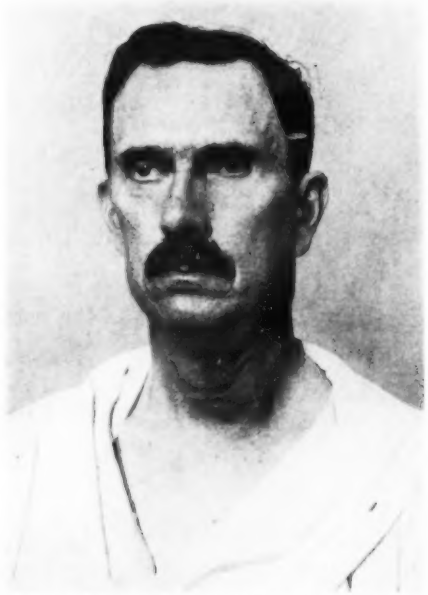

FIG. 5.—Case 1. Two weeks after the operation. Although a portion of the vagus nerve was removed, the voice was not changed following the operation.

FIG. 6.—Case 2. Age 37. Duration of tumor 4 years. Skin sallow. Note the tense sterno-mastoid muscle. Carotid artery very superficial. There was marked bulging of the right pharyngeal wall.

FIG. 7.—Specimen from Case 1. Weight 190 grams. The blood vessels are very prominent.

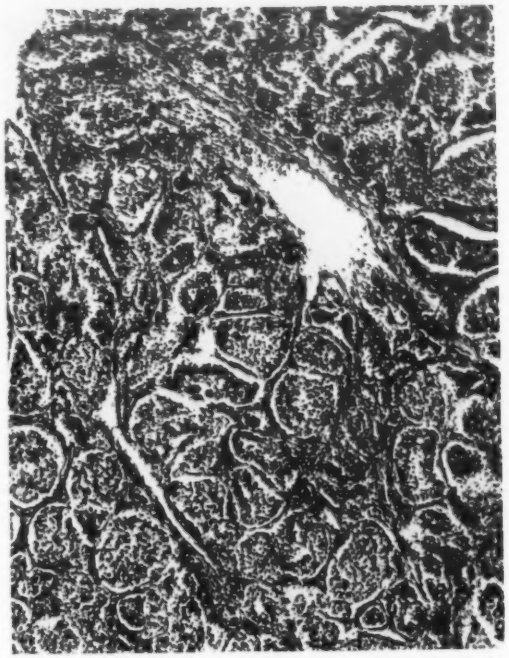

FIG. 8.—Photomicrograph from the specimen of Case 1. Very vascular. Note the alveolar arrangement and hyperplastic appearance. The nests of cells resemble the "cell balls" of the normal carotid body.

FIG. 9.—Specimen from Case 2. Weight 57 grams. The dotted line represents the bifurcation of the common carotid artery. *A*, groove for internal carotid artery; *B*, groove for external carotid artery.

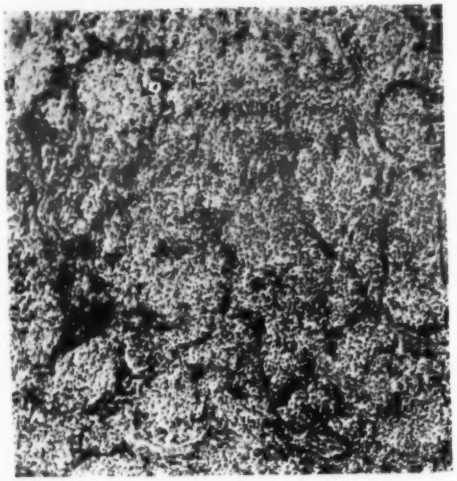

FIG. 10.—Case 2. Photomicrograph. The alveolar arrangement is evident. The cells are small. There is considerable round cell infiltration. This tumor received radium treatment over a period of several months.

FIG. 11.—Case 3. Specimen. Yellowish white center, reddish black periphery.

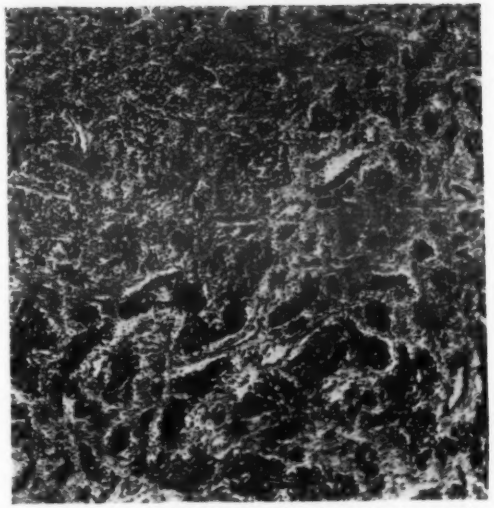

FIG. 12.—Case 3. Photomicrograph. Very active hyperplasia; cells proliferating and infolding into blood spaces. The blood spaces are filled with red blood cells.

of the growth, and its branches were easily palpable. The temporal pulse was equal on both sides. There was no disturbance of the circulation or nerve supply to the right side of the face. The pupils were equal and reacted normally.

The tumor had obliterated the right fauces and had pushed the pharyngeal wall across the midline of the throat and the soft palate forward. The mucous membrane was intact and was not attached to the growth. From the outer surface of the tumor to the swelling on the inner side of the neck the distance was 8 cm. There was slight atrophy of the right side of the tongue and it deviated a little to the right when protruded.

There was complete paralysis of the right vocal cord.

May 3, 1919. At the operation I was able to free the tumor anteriorly and from the mucous membrane of the throat. It was necessary to remove the sterno-mastoid muscle which seemed to be attached to the tumor. The carotid artery, jugular vein and vagus nerve were so inextricably bound up in the tumor that I could not free them. After dividing these vessels and the nerve below it, the operation was completed rapidly, although I had a little difficulty in securing the vessels at the base of the skull where they emerged from the tumor substance. It was necessary to cut the hypoglossal nerve and to remove part of the digastric muscle.

When the vessels and vagus nerve were divided the patient had some alarming symptoms. The pulse became slow; respirations ceased for a few moments and then became markedly Cheyne-Stokes in character. The right side of the face to exactly the midline of the forehead, nose and lips became absolutely blanched, while the left was pink. The right pupil was dilated. Recovery was gradual, the periods of apnœa and the blanching of the face persisting for almost an hour.

The convalescence was complicated by the development of measles on the 10th day, and also by the discharge of some fluid from the wound. The character of this fluid was a light yellow serum so that the dressings were stained a golden yellow. As no tumor was left behind it was difficult for me to explain the yellow fluid. There was a mild infection, and the tissues about the wound reacted by exuding a yellow fluid almost like bile. This drainage persisted for four weeks.

The patient's voice was not affected, for she had already accommodated for a paralysis of the right cord before operation. The right pupil remained a little small. For a time there was some coughing and difficulty in swallowing due evidently to the paralysis of the hypoglossal and vagus nerves. The tongue deviated to the right on protrusion.

The tumor was pigmented, being a brownish color at the periphery and yellowish in the center. It was somewhat spongy and elastic. Weight, 57 gm. (Fig. 9). Measurements 7 x 5 cm. In the microscopical sections (Figs. 8 and 10), the tumor cells showed an alveolar arrangement. The connective-tissue septa were infiltrated with round cells and in some areas, with polymorphonuclear cells. This reaction may have been caused by the radium. There were numerous large blood vessels.

November 5, 1919. The patient returned on this date for observation. I was immediately struck by the appearance of her skin which was white and normal (she voluntcered the information that she and her friends had noticed the improvement in her color), whereas at the time of operation it was dark and yellowish. There was no recurrence, and her only discomfort was an occasional coughing spell when eating. The right pupil was two-thirds the size of the left and reacted normally. In the throat the tonsillar space on the right side was deep, but otherwise appeared normal. No pulse could be felt in the right temporal artery. There had been no cerebral disturbance.

CASE 3.—(Surgical No. 33032.) A white man, 47 years old, was admitted to The Johns Hopkins Hospital October 13, 1913, complaining of a mass in the right side of his neck. His family and past histories were unimportant in so far as they related to his trouble.

For 35 years there had been a swelling in the right side of his neck. Until two years before consulting Dr. Halsted it had remained about the size of a cherry. Then it had increased gradually for a year and a half, whereas for the last six months its growth had been more rapid. Six weeks before our observations began, the growth was explored by his local doctor who found the tumor so vascular that he did not think it safe to attempt its removal. After that the patient's voice had become hoarse and the speech more difficult.

There was a tumor in the upper right side of the neck descending to within 4 cm. of the clavicle. It was under the sterno-mastoid muscle and extended more into the anterior triangle of the neck than behind the muscles. The mass was roughly oval, measuring 10 cm. vertically and 8 cm. transversely. The skin was normal and freely movable except that the scar of the previous operation was attached to the tumor which appeared to be slightly nodular and very firm. Over its outer and anterior surface ran the carotid artery whose pulsations were easily seen and felt. There was no expansile pulsation of the swelling. Neither could a thrill nor bruit be detected in it.

There was a ptosis of the right upper eyelid and a constriction of the right pupil. The patient insisted that these conditions had been present since childhood, and that they had no connection with the development of the tumor.

There was complete paralysis of the right vocal cord.

The operation was difficult and rather tedious on account of the numerous bleeding points. The vagus nerve was so caught in the growth that it had to be divided early in the operation. An opening was accidentally made in the internal jugular vein and there was a definite suction of air before the vessel was clamped and ligated. The artery which ran over the anterior part of the tumor was freed and thrown mesially. At about this stage in the operation the patient became somewhat cyanotic and developed a rapid pulse. The tumor which extended well up to the base of the skull, but which by this time was well freed, was quickly removed. The patient's condition did not, however, improve and death came at about the time the wound was closed. The operator felt that death was connected with the stimulation of the vagus nerve and possibly, also, with the suction of the air into the jugular vein. There was very little loss of blood.

The specimen was a slightly lobulated mass measuring 7 x 4 x 3.5 cm. It was a dark blood color. On section the center of the tumor was rather white and fibrous and sent radiating strands of this tissue into the dark red, cellular periphery (Fig. 11). The tumor was rather spongy and on pressure a frothy bloody fluid came from the cut surface. The histological structure was so typical of the tumors that are often called perithelial angiosarcomas (Fig. 12) that, at that time, a diagnosis of a perithelial or endothelial angio-sarcoma of the neck was made. That the tumor was associated with the carotid body did not then occur to us. As we now look back on the case everything about it is typical, both clinically and pathologically, of carotid body tumors. The color, the structure, the position in the neck and its relation to the nerves and blood vessels of the neck leave no doubt that the growth originated in the carotid body.

DISCUSSION

The discussion of a condition so well described in the literature is scarcely justifiable unless something new can be said. There is probably not yet any unanimity of opinion as to the origin of the carotid gland. It seems to be a question as to whether it comes from the endoderm, mesoderm, or ectoderm. Much has been written about this subject. Kohn believes that the sympathetic ganglia and carotid body arise from

the same type of cells. Such an origin is the most generally accepted view. There seems to be no doubt that it belongs to the chromaffine system and its relation to the sympathetic nervous system seems to be very like that which exists between the medulla of the suprarenal body and the sympathetic nerves.

1. *Pathology.*—Various authors have regarded "carotid body tumors" as peritheliomas, endotheliomas, adenomas, epitheliomas, perithelial angio-sarcomas, etc. Slight variations in the histological structure have no doubt led to these differences of nomenclature. However, the behavior of all of these tumors and the similarity in general of their gross and histological appearance, would seem to indicate that "tumor of the carotid body" has been regarded as a nomenclature of sufficient pathological specificity. The description of their behavior in life, their gross appearance and the general similarity of the histological pictures leave no doubt that under the appellation of "carotid body tumor" a *certain* pathological condition of the carotid body has been well described. The tumors reported in this paper correspond to the accepted description of "carotid body tumors." Many conditions described as carotid body tumors have been discarded by various authors because they did not correspond to this particular description. "Potato tumors," as described by Hutchinson and Gilford, do not come within the scope of the accepted meaning of "carotid body tumors." Certainly, the tumor described by Wooley and Fee appears to have been an aberrant thyroid.

(a) *Hyperplasia.*—But, must we not ask ourselves if the carotid body may not be the seat of various pathological conditions? May not the carotid body, like the thyroid, be subject to changes similar to those that occur in the thyroid or any other gland? One would not speak of exophthalmic goitre or a local hyperplasia of the thyroid gland as a "thyroid gland tumor." It seems to me that we are doing this thing, however, in speaking of "carotid body tumors." The histology of so-called "carotid body tumors" appears to bear the same relation to the structure of the normal carotid gland as the histology of exophthalmic goitre bears to the normal structure of the thyroid gland. In the case of carotid body tumors differences of structures have no doubt given rise to the differences of opinion as to the best name for these tumors, as perithelioma, endothelioma, angio-sarcoma, alveolar sarcoma, adenoma, perithelial angio-sarcoma, etc. Differences in the amount of stroma, and parenchyma of cases of exophthalmic goitre do not lead any more to a confusion of terms—we speak of hyperplasia of the thyroid gland. I believe that it would simplify matters to regard the now accepted carotid body tumors as a local or general *hyperplasia* of the carotid gland, the variations in the amount of stroma and parenchyma accounting for the slight differences in the photomicrographs that appear in the literature.

(b) *Adenomata.*—It may be said that a hyperplastic condition would most likely involve both carotid bodies. Only a few such cases have been recorded. It would obviously be very difficult to determine whether any condition arising in a structure so small as the carotid body began in part or all of it. If "carotid body tumors" are due to a hyperplasia of a part of the gland, adenomata would be a more appropriate term to use. The unilateral "carotid body tumors" that have been described may have been local hyperplasias—adenomata—while the bilateral cases may have been true hyperplasias of the entire substance of both glands.

(c) *Malignant Tumors.*—Although it seems clear that most authors have tried to limit the name "carotid body tumor" to a specific local or general hyperplastic condition of the gland, it is certain that malignant changes in a benign hyperplasia, or true primary malignant tumors have been observed. Da Costa says that carotid body tumors may become maligant. And why should not in some cases a hyperplasia or adenoma of the carotid body become malignant? Similar changes are seen in the thyroid, and perhaps, occur in the adrenals or in the hypophysis. If one admits that the "potato tumors" described by Hutchinson and Gilford developed in the carotid body, then it seems certain that we have described for us primary malignant conditions of the carotid body. Gilford describes two cases that were apparently sarcomas, while his third case seems to have been a carcinoma. They were rapidly fatal, non-pigmented cellular tumors whose structures varied markedly from that of the carotid body hyperplasia. So hyperplasia, hyperplasia with malignant change, sarcoma and carcinoma of the carotid body have all been reported. Confusion has been caused by trying to limit the term "carotid body tumor" to mean the pigmented slow-growing tumor which appears to be certainly a hyperplasia or adenoma of the normal carotid body. Other conditions, such as cysts or myxomas, may have been seen by surgeons but not recognized as arising from the carotid gland.

Without going further into the pathology of adenomata of the carotid gland which are very definite lesions and which have been so admirably described by many authors as "carotid body tumors," my remarks will be confined to the discussion of some observations which may have a bearing upon the diagnosis, the treatment, and possibly the function of the carotid gland.

2. *Diagnosis.*—Keen, who was the first American to write at length about these tumors, has given us the very best illustrations and descriptions of their pathology. He speaks of twelve points which may be helpful in the making of a proper diagnosis: (1) The position at the bifurcation of the carotid artery, (2) movability laterally but not vertically, (3) ovoid in shape, (4) smooth and not lobulated, (5) single, (6) transmitted pulsation, (7) bruit and thrill, (8) bulging of the wall of the pharynx, (9) pupils occasionally constricted, (10) slow growth, (11) long duration, and (12) a rather firm elastic consistency. Speaking negatively he says they are: (1) Not tender, (2) not painful and (3) the deformity is the main complaint. Funke and others call attention to numerous very similar characteristics that ought to help in the making of a correct diagnosis.

Yet the fact remains that it is very unusual for these tumors to be diagnosed correctly before operation. Reclus

and Chevassu, Kopfstein and Maydl, Da Costa, Kocher (in the case reported by Licini), Boni, Lilienthal, and Winslow have correctly made a diagnosis of carotid body tumor before operation. Most of these authors, however, have profited by mistakes in their first cases and thus have diagnosed correctly those that they met with subsequently. An important point upon which Kocher based his diagnosis of the case reported by Licini was the fact that the carotid artery seemed to run through the tumor. Funke says that the large vessels of the neck may be caught by these growths and pushed laterally.

(a) *Position of the Artery.*—Thus, what ought to be a great help in the differential diagnosis of these tumors, is touched upon very lightly in the literature. I know of no other growth of the neck which catches, fixes and carries the carotid artery with it. Enlargement of the lymphatic glands usually leaves the artery in its course or perhaps rolls it a little anteriorly or posteriorly. Large benign thyroid conditions always throw the carotid artery posteriorly, so that in large colloid goitres it may be felt as a freely movable vessel and not far from the midline of the neck. Malignant thyroid tumors may invade, but do not distort, the course of the common carotid artery. So, branchial cleft cysts, hygromas and other benign tumors of the neck may roll the artery so that it becomes a slightly displaced, freely movable vessel.

Gomez gives illustrations of the various positions of the carotid gland. The commonest position is on the mesial side of the bifurcation of the common carotid artery. Even the six variations are on the mesial and posterior side of the artery, and within its sheath, so that any enlargement would catch this vessel. In most of the illustrations of carotid body tumor (see Keen and Steindl) the tumor is lodged in the bifurcation of the artery like a nest in the fork of a tree. The groove caused by the internal and external carotid arteries are, as in our cases, on the lateral or antero-lateral aspect of the tumor. Often only a little of the tumor is represented as projecting between the forks of the vessel. In large carotid body tumors the sterno-mastoid muscle is pushed laterally so that from the tumor to the clavicle it may stand out as a rather tense cord; and the common carotid artery or its branches may be seen and felt very superficially, running over the surface of the tumor, but cannot be displaced (Fig. 6).

(b) *Effect on the Vagus Nerve and Pharynx.*—When carotid body tumors attain a moderate size it is usual for them to cause a bulging of the pharyngeal wall, which may even be pushed to or beyond the uvula. Some observations on Case 1 of this report lead us to believe that it is the restraining influence of the carotid artery and sterno-mastoid muscle that tends to make the tumor grow mesially. Paralysis of the recurrent laryngeal nerve has been noted frequently and was present in all three of our cases. This fact together with the relatively infrequent occurrence of disturbances of speech following operations would lead me to believe that the carotid body tumors of considerable size do usually cause a paralysis of the vocal cord. It is interesting that in two of our cases the patients gave no history of ever having disturbance of speech, and yet the routine examination of the throat showed that both of them had a paralysis of the vocal cord on the side of the tumor. Apparently, a very gradual paralysis of the recurrent laryngeal nerve may not affect the voice very noticeably. Perhaps in a couple of cases the hypoglossal nerve has been paralyzed by these tumors.

(c) *Aneurysms.*—Numerous cases of very vascular adenomata of the carotid body, as in Case 1, have been diagnosed as carotid aneurysms. A thrill and bruit, and a definite expansile pulsation may be very misleading. There is no doubt that the pulsation of these tumors may be definitely expansile. This was true in Case 1, both before and after ligation of the common carotid artery. Malignant or pulsating exophthalmic goitres have been mistaken for aneurysms. The mistake would be more common if the thyroid gland were situated at the bifurcation of the common carotid artery.

3. *Function.*—Nothing is known about the function of the normal carotid body, nor have any functional disturbances been described in connection with its hyperplasia. In the two cases upon which I operated, the pigmentation of the body has been a striking clinical observation. Case 1 showed an erythematous flush over the neck, a suffusion of the face and a yellowish dark color of the entire body. Case 2 showed a light lemon yellow color of the entire body. The pigmentation in both of these cases cleared up completely after the removal of the tumors. In both cases the adenomata were completely removed. The wound of Case 2, however, became slightly infected and drained a light bile-colored fluid for almost four weeks. Were the body juices saturated with a chromaffine substance? These patients were the opposites of exophthalmic goitre patients—their actions were slow, their speech deliberate; they were not nervous and there was no tachycardia. The pigmentation was certainly associated with the hyperplasia of the gland. The slow actions and slow queer speech may always have been characteristic of my patients and not due to the growth.

4. *Treatment.*—Surgeons cannot be proud of the results of the surgical treatment of carotid body tumors. A mortality of between 27 and 30 per cent, and a morbidity nearly as high, should make one hesitate before operating on these conditions. Most of these patients have been operated upon for cosmetic reasons and probably would not have submitted to an operation had they known that in the vast majority of cases it was necessary to divide the carotid artery, the jugular vein, the vagus and hypoglossal nerves. Pneumonia, hemorrhage, cerebral anemia, and infection are given, in the order of their importance, as the causes of death. Pneumonia is thought to be favored by section of the vagus nerve and, if this be so, will probably remain the greatest cause of death following operations upon tumors of the carotid gland. In the present age surgeons pay so much attention to hemostasis that deaths from hemorrhage would not be likely to occur. Dr. Halsted has suggested that deaths and paralyses due to cerebral anemia may be lessened or prevented by producing a gradual occlusion of the artery by a metal band before extirpating the

tumor, a procedure which would insure to the brain a better collateral circulation when the major operation is done.

The advisability of surgical treatment of tumors of the carotid body has been questioned by eminent surgeons. Keen, Da Costa, Reclus and Chevassu advise against operation, when the tumor is large and it is almost certain that its removal will necessitate sacrificing the carotid artery, jugular vein and vagus nerve. Small tumors that can be freed from these important structures should be removed. Preliminary partial or complete ligation of the common carotid artery will lessen the danger of cerebral disturbances that may follow the extirpation of large tumors. Yet after a preliminary ligation of the artery the control of hemorrhage may be very difficult. In the first case reported in this paper the tumor, which is the largest on record, was successfully removed six years after the ligation of the common carotid artery, but the control of hemorrhage was one of the most difficult surgical problems I have met with. That an adenoma or hyperplasia of the carotid body should be removed in order to avoid the danger of its becoming malignant is not well proven. The very long duration (1 to 40 years) of the growths in the cases reported, would seem to indicate that a carotid adenoma is not particularly prone to become malignant. For truly malignant tumors of the carotid gland, very radical operations should be performed. In the one, or possibly two cases, of an enlarged carotid body in which malignancy has ensued, the changes in the character of the tumor have been very like those observed when a carcinoma develops in an adenomatous or colloid goitre.

(a) *Decompressive Operation.*—Experience with Case 1 leads me to suggest what might be called a decompressive operation. After a division of the sterno-mastoid muscle and the simple ligation of the common carotid artery the tumor which had previously projected across the midline of the pharynx came out laterally and posteriorly, so that six years later the pharynx appeared normal. When, therefore, a surgeon does not feel that he can or ought to remove a hyperplastic carotid body it may be feasible to cut the sterno-mastoid muscle, and possibly to ligate the common carotid artery, in order to relieve an encroachment upon the pharynx, and to facilitate the removal of the growth at a later date by allowing it to become more superficial.

SUMMARY

1. The slow growing pigmented tumor of the carotid gland, heretofore described as "carotid body tumor" is a simple hyperplasia of a part or all of the normal gland; it should be designated as an adenoma or hyperplasia of the carotid body. In rare instances a malignant condition may develop in it.

2. A "potato tumor of the neck" may be a primary sarcoma or carcinoma of the carotid body.

3. The relation of the common carotid artery to enlargements of the carotid gland ought to help us in arriving at a correct diagnosis. This artery is caught and carried laterally or anteriorly so that it and its branches may often be readily felt on the surface of the tumor.

4. A bulging of the pharyngeal wall and a paralysis of a vocal cord are frequently observed in an enlargement of the carotid body. The paralysis may be detected only by direct examination of the cords, inasmuch as disturbances of speech do not usually occur.

5. Yellowish pigmentation of the body, flushing of the head and neck and a slow, somewhat apathetic state of mind may result from hyperplasia of the carotid gland.

6. The mortality of operations for hyperplasia of the carotid body has been very high. Preliminary ligation, partial or complete, of the carotid artery, and careful hemostasis at the second operation may reduce it materially.

7. In some cases in which an operation is imperative on account of the size of the growth it may be wiser to do a decompressive operation than to attempt extirpation of the tumor. Then, after the tumor dislocates laterally and becomes more superficial, its removal will be easier and safer, particularly if the artery has been tied at the time of decompression.

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A STUDY OF THE HÆMODYNAMIC REACTIONS OF THE CEREBROSPINAL FLUID AND HYPOPHYSEAL EXTRACTS

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SYNOPSIS

1. Introduction.
   Review of literature.
   Presupposition of hæmodynamic substance in cerebrospinal fluid.
2. General plan of and methods employed in this and in previous researches.
3. Protocols with experimental data.
4. Comparison of hæmodynamic, glycogenic and diuretic effects of cerebrospinal fluid and hypophyseal extracts.
5. Summary and inference.
6. Nature of depressor substance.
   a. Relation to choline.
   b. Effect of stimulation of hypophysis on blood pressure.
   c. Effect of stimulation of superior cervical ganglion.
   d. Similarity to histamine.
7. Conclusion.

Although the existence of the pituitary gland had been vaguely known for several centuries, it remained for Marie in 1888-1889 to give impetus to the closer study of the gland by associating certain anomalies of skeletal growth with tumor or hypertrophies of that structure. In 1895 Schaefer and Oliver[1] showed that its infundibular lobe possessed a blood pressure raising substance, and since that time a mass of literature has appeared concerning the structure and physiology of the gland as one of the endocrine series. Most conflicting statements of its power as a hæmodynamic, glycogenic, diuretic, galactagogic and peristaltic agent have been made and have added confusion to our meager knowledge of the intercorrelated action of the ductless glands. Granting that it has a specific internal secretion, the method and manner of its production and disposition, its chemical composition, its characteristic properties, its relation to the body economy in health and disease are still fruitful problems for future investigation.

Herring,[2] in 1908, advanced the theory that the secretory activity of the posterior lobe of the hypophysis, represented principally by faintly staining hyaline bodies, passes by way of the infundibular stalk and finds its way between the ependymal cells into the cavity of the third ventricle where it enters into solution with the cerebrospinal fluid and finds its way into the blood stream of the dural sinuses.

Cushing and Goetsch,[3] in 1910, confirmed these findings, basing their evidence (1) on the histological picture of the increase of and migration of these hyaline bodies towards the ventricle when the gland is subjected to various operative procedures and (2) on the supposed presence of a hæmodynamic substance in the cerebrospinal fluid giving reactions quite comparable to those due to posterior lobe secretion.

These conclusions were subsequently questioned by Edinger[4] (1911) who by histological studies and by injection methods was led to believe that the hyaline bodies pass along the stalk to a certain zone where the infundibular process joins the tuber cinerium and the interneurogliar pathways abruptly cease, and that the hyaline bodies do not enter the ventricle.

Crowe and Evans (unpublished communication) by intravitam staining, moreover, have shown that the posterior lobe stains deeply up to a certain and perhaps similar zone beyond which the tuber cinerium and brain remain unstained.

Lewis, Miller and Matthews[5] (1911) were unable to demonstrate the presence of a pressor substance in the infundibular stalk, a part of the gland in which the hyaline bodies are presumably present; this finding is opposed to Herring's views unless the bovine gland has an anatomical arrangement different from the canine.

The observations of Cushing and Goetsch (1911) seem to show that concentrated cerebrospinal fluid from various clinical cases, when injected intravenously into rabbits and dogs, produced hæmodynamic reactions with increased amplitude of the pulse, similar to those from posterior lobe extract injections. Moreover, diuresis was almost invariably evoked; peristalsis was often stimulated with resultant catharsis; the smooth muscle of the uterus and bladder was brought into contractile states, and glycogenic effects were produced with resultant glycosuria. Subsequently Carlson and Martin[6] (1911), using somewhat different methods, concluded that cerebrospinal fluid, from dogs at least, had no pressor or depressor effect upon the canine circulation, and that the intravenous injection of whole gland, anterior or posterior lobe of the pituitary body, does not produce sugar in the urine. These are definitely contradictory findings and form the subject with which this paper is mainly concerned.

The observations of Cushing and Goetsch were based primarily upon the reaction obtained by the intravenous injection of concentrated solutions of cerebrospinal fluid of human origin. They usually employed 2 c. c. of a 30-1 or a 20-1 concentration and contrasted the results with the reactions furnished by small amounts of whole gland or individual lobe hypophyseal extracts. It is well to note that in this procedure there was employed a large amount of stimulating substance per unit volume of fluid injected. The observations of Carlson and Martin, on the other hand, were based upon the intravenous introduction of a large amount of unconcentrated canine cerebrospinal fluid into an animal of the same species, the body fluid volume being kept constant by a pre-

liminary bleeding of the animal in amount equal to the fluid injected. Under these circumstances there was utilized a small amount of stimulating substance per unit volume of fluid injected. To determine the glycogenic effect they introduced intravenously an extract made from 1-10 whole canine glands into another dog without producing glycosuria.

It is quite obvious that the conflicting observations in the above researches are due to the different methods employed and pertain to the degree of concentration of the injected fluid. Undoubtedly the concentration of cerebro-spinal fluid of human or bovine origin in a proportion of 30-1 or 20-1 produces a strongly hypertonic, well-nigh saturated solution, and Carlson has rightly raised the question regarding the interpretation of hæmodynamic reactions caused by the introduction even of small amounts of such concentrated solutions into small animals. In acceptance of this criticism it was thought advisable in this investigation to make an "artificial spinal fluid" free from organic substances and use this as a control for the concentrated spinal fluid.

Briefly stated the object of this present investigation is a study of the physiological effects of intravenous injections of unconcentrated and concentrated spinal fluid, human, bovine and artificial, in contrast with similar injections of hypophyseal extracts, anterior lobe, posterior lobe, pars intermedia and whole gland, in the hope of reaching some definite conclusion regarding the presence or absence of the pituitary secretion in the cerebrospinal fluid.

Preparation of Fluids

Human Spinal Fluids.—These were obtained during operation or clinical examination from 39 separate cases by ventricular or lumbar puncture. Most of these specimens, as seen from the appended list, were from patients suffering from conditions with obstruction to the cerebrospinal outflow and yielded on various occasions spinal fluid in considerable amounts. Carlson has intimated that these were pathological fluids but in the absence of any specific infective process one scarcely knows what constitutes a pathological cerebrospinal fluid. It is improbable that any long-standing obstruction would produce any marked chemical or organic change in the fluid. The fluid of internal hydrocephalus, for example, is generally considered to be normal cerebrospinal fluid. The fluid used in these experiments was collected in sterile bottles and, if not used immediately, sterilized at low heat and kept in a dark place. On prolonged standing it sometimes became slightly opalescent due no doubt to hydrolytic cleavage of some of the organic material. When used in concentrated form it was evaporated either on the water-bath or under reduced pressure *in vacuo;* the two different methods of concentration evidently had no appreciable effect upon the resultant concentrate as far as the subsequent physiological reaction was concerned. The sources of the fluid are given in Table 1.

TABLE 1

Human Spinal Fluid

Fluid No.	Diagnosis	No. fluids	Amount c. c.	Source of fluid
1 R-k ...	Cerebellar tumor	9	765	Ventricular.
2 A-n ...	Epilepsy	2	150	Ventricular.
3 S-r....	Cerebellar tumor	1	60	Ventricular.
4 S-z....	Cerebellar tumor	1	50	Ventricular.
5 G-z ...	Epilepsy	2	70	Lumbar and ventric.
6 K-t ...	Infundibular tumor	1	60	Ventricular.
7 C-d ...	Internal hydrocephalus	2	50	Lumbar.
8 G-s ...	Hypopituitarism	1	60	Lumbar.
9 W-l ...	Hypopituitarism	1	25	Lumbar.
10 F-y ...	Cerebral tumor	1	50	Lumbar.
11 C-s....	Cerebellar tumor-hydrocephalus.	2	120	Lumbar and ventric.
12 S-y ...	Temporal lobe tumor	8	410	Lumbar and ventric.
13 B-r ...	Temporal lobe tumor	6	460	Lumbar and ventric.
14 Be-r ..	Cerebellar tumor	4	120	Lumbar and ventric.
15 S-y....	Pituitary tumor	1	50	Lumbar.
16 S-h	Cerebellar tumor	2	300	Ventricular.
17 D-r	Hydrocephalus	4	200	Ventricular.
18 K-z	Hypopituitarism	1	30	Lumbar.
19 S-w	Pituitary tumor	1	30	Lumbar.
20 T-t....	Cerebellar tumor	1	50	Ventricular.
21 H-m ..	Pontine tumor	1	100	Ventricular.
22 N-s	Hydrocephalus	4	240	Ventricular.
23 K-z	Hydrocephalus. Pineal tumor...	2	80	Lumbar and ventric.
24 M-k....	Hydrocephalus	8	450	Ventricular.
25 T-w....	Hydrocephalus. Pineal tumor?..	4	120	Ventricular.
26 G-n	Cerebellar tumor	6	240	Ventricular.
27 G-n-n..	Cerebellar tumor	1	40	Ventricular.
28 P-ns ..	Cerebral tumor	4	160	Ventricular.
29 C-y	Cerebellar tumor	1	40	Ventricular.

Bovine Spinal Fluid.—Large amounts of sterilized bovine cerebrospinal fluid were obtained through the courtesy of Armour & Co. and of Parke Davis & Co. The fluid from the former was slightly dark brown in color and had a small flocculent precipitate; that from the latter was clearer and lighter in color. Both were sterile on culture. One portion of each fluid was evaporated down to the required concentration and the other portion evaporated to dryness, the residue finely pulverized and weighed amounts of the powder, in aqueous solutions, used for subsequent injections.

Artificial Spinal Fluid.—These were solutions containing the inorganic salts found in normal cerebrospinal fluid. They were made according to the formula given by Halliburton[7] (Sp. fluid A) and Meztrezat[18] (Sp. fluid B.).

Fluid A		Fluid B	
Water	1000.	Water	1000.
NaCl	7.098	NaCl	8.362
KCl	0.33	KCl	0.397
		$CaCl_2$	0.186

The NaCl to KCl ratio was 21 to 1 in both solutions. At times there was added the normal dextrose content of 0.07 per cent. These solutions were practically Locke's solutions.

Pituitary Preparations.—Commercial pituitary extracts were obtained likewise from Armour & Co., Parke Davis & Co., or were bought in the open market. Inasmuch as such preparations were found to differ markedly in their effect, care was taken to use the same preparation on the same animal in order to get comparative results. Absolutely fresh bovine extracts were made from glands secured from the local abattoir and several hundred glands were sent to the laboratory packed in ice by Armour & Co. From these glands all capsular and adventitious matter was carefully removed and the tissues were carefully separated preliminary to making extracts of (1) whole gland, (2) anterior, (3) posterior lobe, (4) pars intermedia and (5) the colloid material found in the interlobular cleft. These different portions of tissue were then separately ground with sand and with a small amount of physiological salt solution. The extracts in each case were separated out by passing through a Buchner press and evaporated to dryness either by pan evaporation or under reduced pressure *in vacuo*. The dried preparations were then finely pulverized and weighed amounts were separately used for injections. In this manner 625 glands furnished 60.2 gms. of anterior lobe, 16.2 gms. of posterior lobe and 3 gms. of pars intermedia, while 100 glands furnished 14.8 gms. of whole gland extract. On several occasions fluid extracts were made from fresh material and used immediately for injection purposes.

Animals.—The animals used were mainly rabbits and dogs. It was found unnecessary to anæsthetize the former for the observations, but ether and occasionally chloretone was employed for the dogs. Pulse tracings were taken from the carotid and the injections were made into the jugular and occasionally into the saphenous vein. Urine flow was counted in drops from a small glass catheter passed into the bladder through the urethra. In order to have sufficient free available glycogen and plenty of body fluid for diuretic effects, care was taken to have the animal well fed with carbohydrate and with plenty of fluid before the experiment. Injections consisted of 2 or 3 c. c. in volume. This amount was found to have no appreciable effect upon the blood pressure.

Results of the injections are given in the protocols on pages 188-191.

As can be seen from the abbreviated protocols, the resultant reaction obtained from the injection of cerebrospinal fluid, artificial spinal fluid, anterior, posterior lobe, pars intermedia and whole gland of the hypophysis are extremely variable, depending not only upon the species of animal used but also upon the individual animal itself. All reactions fall quite readily in the above groupings, considering any change below 10 mm. of mercury, a low limit, as negligible or negative. The results of injection of pituitary extract, definite as such reactions are supposed to be, are in fact so variable that one is led to doubt somewhat the existence of a specific secretion. It is also claimed that successive injections render the animals insensitive to the reaction, and as a consequence, single injections have been used in several researches. That this is probably an overstatement is readily seen from results in this comparative study in which as many as 8 or 10 injections have been given in the same animal with a gradual change in the reaction. It is quite evident that an erroneous impression can be obtained from a single chart or injection, and this no doubt accounts for the marked confusion upon the subject in the literature. Definite conclusions can only be obtained by the comparative study of a series of injections in the same and in many animals.

Discussion of Results of Injections

1. *Cerebrospinal Fluid Injections.*—Moderate concentrations of human and bovine spinal fluid when injected intravenously usually cause a slight depressor effect followed by a more or less prolonged pressor effect. With increase in concentration these effects are more pronounced. These reactions are usually of a transient character but on marked concentration the effect may be prolonged. Record 1 * shows clearly the augmentation of depressor and pressor effect with increase in concentration of fluid, while Record 2 shows a typical response from a 20-1 concentration of human spinal fluid. This is very similar to the effect described by Cushing and Goetsch in their original article and considered by them as indicative of the presence of a posterior lobe secretion.

2. *Artificial Spinal Fluid Injections.*—Intravenous injections of this fluid in concentrated form give also usually a depressor response quite similar to that from similar concentrations of human and bovine spinal fluid. Records 3, 3-a and 4 give quite typical responses to injections of artificial spinal fluid contrasted with human spinal fluid. Records 5 and 6 show a similar contrast between artificial fluid and bovine spinal fluid.

3. *Hypophyseal Injections.*—The responses to injections of hypophyseal extract are very variable both when used as successive injections in the same animal or in different animals and we have a varied assortment of confusing reactions and blood pressure curves. The classical posterior lobe reaction is supposed to consist of a transient depressor effect followed by a long enduring pressor response persisting for some 10 minutes and frequently over 20 minutes. Such curves are shown by Records 7, 8 and 9, which reveal a moderately good response to posterior lobe injections in an animal which gives practically negligible responses to injections of concentrated artificial and human spinal fluid. Record 10 also shows another posterior lobe response in which the depressor effect is practically missing. That these glandular manifestations as far as the blood pressure raising effect is concerned may be extremely variable is readily seen by a series of injections and reactions in four dogs, R_2, S_2, T_2, V_2, essentially similar in all respects as far as weight and outward general condition are concerned. Records 11 to 22 show a series of three quantitatively similar injections into each animal of anterior, posterior and pars intermedia, extracts carefully made in the laboratory from the respective parts of the ox gland. The varied results obtained from identical injections into similar animals clearly demonstrate the difficulty of ascribing specific effects to differentiated

* To economize space, the blood pressure curves are presented in outline, drawn and reduced from the kymograph tracing.

PROTOCOLS

Date	Case	Injections				Blood pressure effects—mm. Hg.				Urine		Remarks
		No.	Spinal fluid	Art. fluid	P. lobe	Negative	Pressor	Depressor	Dep. and pres.	Diur.	Glyco.	
3-3-11	Rabbit C.	1	2 c. c. (10-1)	.....	.....	.....	138-154	.....	.....	.....	.....	Vent. fluid—Roebuck.
		2	" (10-1)	.....	.....	.....	140-156	.....	.....	.....	.....	
		3	.....	.....	1/20 gm.	.....	86-186	.....	.....	.....	.....	No urine.
		4	.....	.....	1/80 "	106-106	.....	.....	.....	.....	.....	
		5	2 c. c. (10-1)	.....	.....	.....	102-120	.....	.....	.....	+	
3-7-11	Rabbit D.	1	" (10-1)	.....	.....	.....	.....	.....	104- 16-146	Slight.	—	Spinal fluid, ox.
		2	" (1-1)	.....	.....	.....	.....	130-120-130	.....	"	—	" " "
		3	" (2-1)	.....	.....	.....	.....	.....	124-112-136	"	—	" " "
		4	" (3-1)	.....	.....	.....	.....	.....	110- 88-132	+	—	" " "
3-9-11	Rabbit E.	1	" (1-1)	.....	.....	.....	112-122	.....	.....	Slight.	.....	" " "
		2	" (2-1)	.....	.....	.....	.....	.....	116-112-126	"	.....	" " "
		3	" (4-1)	.....	.....	.....	.....	.....	116- 96-126	"	.....	" " "
		4	" (6-1)	.....	.....	.....	.....	.....	128-100-138	"	.....	" " "
		5	" (10-1)	.....	.....	.....	.....	.....	108- 94-138	"	—	" " "
		6	.....	.....	1/20 gm.	.....	100-120	.....	.....	—	+	
		7	.....	.....	1/40 "	.....	.....	.....	78- 50-88	—	+	
3-10-11	Rabbit F.	1	2 c. c. (1-1)	.....	.....	100-108	.....	.....	.....	.....	—	Lumbar fluid—Roebuck.
		2	" (2-1)	.....	.....	102-110	.....	.....	.....	.....	—	" " "
		3	" (4-1)	.....	.....	106-110	.....	.....	.....	—	—	" " "
		4	" (6-1)	.....	.....	104-110	.....	.....	.....	—	—	" " "
		5	" (10-1)	.....	.....	.....	.....	.....	108-100-118	—	—	" " "
		6	" (10-1)	.....	.....	128-134	.....	.....	.....	.....	.....	" " "
		7	" (10-1)	.....	.....	.....	.....	128-110-128	.....	.....	.....	Vent. " "
		8	" (10-1)	.....	.....	.....	.....	102- 90-100	.....	+	+	" " "
		9	.....	.....	1/80 gm.	.....	60-88	.....	.....	+	+	
		10	.....	.....	1/40 "	.....	.....	52- 58-40	.....	.....	.....	
		11	.....	.....	1/20 "	.....	32-42	.....	.....	.....	+	
3-16-11	Rabbit F'.	1	2 c. c. (10-1)	.....	.....	.....	124-140	.....	.....	.....	.....	Lumbar fluid—Roebuck.
		2	" (20-1)	.....	.....	.....	.....	.....	130-124-144	+	+	" " "
		3	.....	.....	1/80 gm. A.	.....	.....	134-112-136	.....	++	++	
		4	.....	.....	1/20 "	.....	.....	.....	.....	—	++	
		5	2 c. c. (40-1)	.....	.....	.....	.....	108-death.	.....	.....	.....	
6-6-11	Rabbit G.	1	" (10-1)	.....	.....	.....	.....	104 82-104	.....	+	+	Vent. fluid—Smith.
		2	" (10-1)	.....	.....	.....	.....	98-80-104	.....	+	+	" " "
		3	" (10-1)	.....	.....	.....	.....	.....	80-66-92	+	+	Spinal fluid, ox.
		4	.....	.....	1/20 gm.	.....	70-100	.....	.....	.....	.....	
6-7-11	Rabbit H.	1	2 c. c. (20-1)	.....	.....	.....	.....	.....	118-10-128	+	+	" " "
		2	" (20-1)	.....	.....	.....	.....	.....	110-86-132	++	++	Vent. fluid—Smith.
		3	.....	.....	1/20 gm.	.....	.....	.....	100-80-120	—	++	
6-8-11	Rabbit I.	1	2 c. c. (15-1)	.....	.....	.....	.....	.....	120-51-168	+	+	Spinal fluid, ox.
		2	" (15-1)	.....	.....	.....	.....	.....	110-74-118	+	+	Vent. fluid—Smith.
		3	.....	.....	1/20 gm.	.....	100-120	.....	.....	—	+	
6-9-11	Rabbit J.	1	2 c. c. (15-1)	.....	.....	.....	136-172	.....	.....	+	—	Spinal fluid—Dyer.
		2	" (20-1)	.....	.....	.....	.....	.....	130-116-152	+	+	" " "
		3	" (20-1)	.....	.....	.....	118-144	.....	.....	++	+	Vent. fluid—Smith.
		4	" (20-1)	.....	.....	.....	.....	.....	110-100-126	+	+	Spinal fluid—Stickley.
		5	.....	(2 c.c. water)	.....	106-108	.....	.....	.....	.....	.....	
		6	2 c. c. (20-1)	.....	.....	.....	.....	106-80	.....	.....	.....	" " Cleland.
		7	.....	.....	1/20 gm.	.....	92-60	.....	.....	—	.....	
		8	.....	.....	1/10 "	.....	.....	78-90-death.	.....	—	.....	
6-10-11	Rabbit K.	1	2 c. c. (20-1)	.....	.....	.....	.....	102-death.	.....	—	—	" " Dyer.
6-12-11	Rabbit L.	1	" (20-1)	.....	.....	.....	.....	88-16-death.	.....	.....	.....	" " "
6-14-11	Rabbit M.	1	" (20-1)	.....	.....	.....	.....	.....	106- 92-138	++	++	Parturient rabbit.
		2	" (12-1)	.....	.....	.....	.....	.....	110-102 140	++	+	Spinal fluid—Wall.
		3	" (15-1)	.....	.....	.....	.....	.....	104- 98-130	++	+	" " Katz.
6-16-11	Rabbit N.	1	" (15-1)	.....	.....	.....	.....	.....	103- 82-121	+	+	" " Dyer.
		2	" (15-1)	.....	.....	.....	.....	.....	103- 95-137	+	+	" " Shaw.
		3	.....	.....	1/20 gm.	.....	.....	.....	80- 72-118	+	+	
6-26-11	Rabbit O.	1	.....	2 c. c. (20-1) water.	.....	.....	.....	.....	84- 66-98	+	—	
		2	.....	.....	.....	82-74-82	.....	.....	.....	—	+	
		3	2 c. c. (20-1)	.....	.....	.....	.....	.....	82- 50-108	+	+	Vent. fluid—Taggart.
		4	.....	.....	1/20 gm.	.....	.....	.....	.....	—	+	
		5	.....	.....	1/20 "	.....	72-86	.....	.....	—	+	
6-27-11	Rabbit P.	1	.....	3 c. c. (1-1)	.....	120-120	.....	.....	.....	.....	.....	
		2	3 c. c. (1-1)	.....	.....	110-104-110	.....	.....	.....	.....	.....	Spinal fluid.—Baker.
		3	.....	2 c. c. (20-1)	.....	.....	.....	.....	.....	.....	.....	Formation of clots with death of animal.
		4	.....	" (20-1)	.....	.....	.....	.....	.....	.....	.....	
		5	.....	" (20-1)	.....	.....	.....	.....	.....	.....	.....	
6-27-11	Rabbit Q.	1	.....	3 c. c. (1-1)	.....	104-106	.....	.....	.....	.....	.....	
		2	3 c. c. (1-1)	.....	.....	102-104	.....	.....	.....	.....	.....	Spinal fluid—Baker.
		3	2 c. c. (20-1)	.....	.....	.....	.....	.....	100-88-116	.....	.....	" " "
		4	.....	2 c. c. (20-1)	.....	.....	.....	92-74-100	.....	.....	.....	No urine obtained.
		5	.....	.....	1/20 gm.	.....	.....	.....	96-88-110	.....	.....	
7-31-11	Rabbit R.	1	.....	2 c. c. (20-1)	.....	110-116	.....	.....	.....	+	+	
		2	2 c. c. (20-1)	.....	.....	.....	.....	.....	104-84-116	+	+	Spinal fluid—Baker.
		3	.....	.....	1/20 gm.	.....	98-120	.....	.....	—	+	
		4	2 c. c. (20-1)	.....	.....	.....	.....	.....	88-76-110	++	++	Spinal fluid, ox.
8-1-11	Rabbit S.	1	.....	2 c. c. (20-1)	.....	.....	.....	.....	124-92-136	Slight.	—	" " "
		2	2 c. c. (20-1)	.....	.....	.....	.....	.....	110-64-194	++	+	
		3	.....	.....	1/20 gm.	.....	94-104	.....	.....	—	+	
		4	.....	.....	1/20 "	.....	64-80	.....	.....	—	+	
8-2-11	Rabbit T.	1	2 c. c. (20-1)	.....	.....	.....	.....	.....	126-78-136	+	—	Vent. fluid—Holtzman.
		2	.....	.....	1/20 gm.	.....	.....	.....	122-86-132	—	—	
		3	.....	2 c. c. (20-1)	.....	.....	.....	.....	106-78-142	—	—	

PROTOCOLS—CONTINUED

Date	Case	Injections				Blood pressure effects—mm. Hg.				Urine		Remarks
		No.	Spinal fluid	Art. fluid	P. lobe	Negative	Pressor	Depressor	Dep. and pres.	Diur.	Glyco.	
8-8-11	Rabbit U.	1	2 c. c. (20-1)						128-110-140	+	—	Vent. fluid—Norris.
		2		2 c. c. (20-1)		130-136				+	—	
		3			1/20 gm.				142-126-152	—	—	
8-9-11	Rabbit V.	1	2 c. c. (20-1)					112-96-116		+	—	" " "
		2		2 c. c. (20-1)				98-78-98		+	—	
		3			1/20 gm.		88-106			—	—	
8-13-11	Dog W.	1			1/20 gm.		116-126			—	—	
		2			1/20 "				110-104-124	—	+	
		3			1/20 "				114- 98-126	—	+	
8-14-11	Dog X.	1	2 c. c. (20-1)					124-114-126		—	+	" " "
		2		2 c. c. (20-1)		122-124				—	+	
		3			1/10 gm.				116-114-134	—	+	
		4		2 c. c. (20-1)		126-126						
8-15-11	Dog Y.	1	4 c. c. (20-1)			160-166				+	+	" " "
		2			1/10 gm.		160-210			—	+	Only few c. c. urine obtained.
		3			1/10 "		152-170			—	+	
		4	2 c. c. (40-1)				158-168			—	+	
		5			2/10 gm.		154-174			—	+	
8-16-11	Dog Z.	1	2 c. c. (20-1)						110 106-122	+		Vent. fluid—Durham.
		2			1/10 gm.				115- 62-178	—		Small amount of urine.
		3		2 c. c. (20-1)					112-102-122	—		
		4			1/10 gm.				112-100-126	—	+	
8-17-11	Dog A-2.	1	2 c. c. (20-1)				140-162			—		Spinal fluid—Anderson.
		2		2 c. c. (20-1)		140-142				—		Only few drops of urine.
		3			1/10 gm.		116-142			—	+	
8-18-11	Dog B-2.	1	2 c. c. (4-1)				161-173			—	—	Spinal fluid—Hall.
		2	" (20-1)			170-176				—	—	" " Stickley.
		3		2 c. c. (20-1)		174-180				—	—	50 c. c. of urine in bladder at end of experiment, 1.6% sugar.
		4			1/10 gm.		160-194			—		
		5			1/10 "				150-142-168	—		
		6			1/10 "				150-130-190	—		
		7			2/10 "		156-192			—	++	
11-24-11	Dog C-2.	1	3 c. c. (13-1)						72-60-84			Spinal fluid—Kurtz.
		2	" (13-1)						70-66 80			Suppression of urine.
		3		3 c. c. (13-1)				50-32-54				
		4			1/20 gm.		42-64					
		5			1/20 "		44-60					
11-27-11	Dog D-2.	1	3 c. c. (13-1)					94-50 94		—		Spinal fluid, ox.
		2	" (13-1)			60-66				—		Spinal fluid=Holtzwig.
		3	" (13-1)					66-40-66		—	+	Spinal fluid, ox.
		4		3 c. c. (13-1)		68-68				—		Suppression of urine.
		5			1/20 gm.		70-90					
		6			1/20 "		64-74					
		7			1/20 "		68-78					
11-28-11	Dog E-2.	1		3 c. c. (13-1)		72-78				—	+	
		2	3 c. c. (13-1)				74-86			—	+	Spinal fluid—Holtzwig.
		3	" (26-1)					60-42-66		—	+	Spinal fluid, ox.
		4		3 c. c. (26-1)		70-72						Suppression of urine.
		5			1/10 gm.		65-108-82					
		6			1/10 "		65-82					
		7	3 c. c. (10-1)					64-38-56				Spinal fluid, ox.
12-4-11	Rabbit F-2	1	2 c. c. (20-1)						92-84-110	+	+	Spinal fluid—Morlock.
		2		2 c. c. (20-1)					98-94-118	++	++	
		3			1/20 gm.				82-70-138	—	++	
		4	2 c. c. (20-1)					78-death.		—		
12-12-11	Dog G-2.	1	4 c. c. (20-1)					104-44-104		+	+	Ox—Alc. filtrate.
		2	" (20-1)					96-80-96		++	++	Ox—Alc. ppt.
		3			1/10 gm.			86-62-68		+	+	Alc. filtrate.
		4			1/10 "		96-114			+	+	Alc. ppt.
		5			1/20 "			80-58-80		+	+	
		6		4 c. c. (20-1)		78-80				++	++	
12-18-11	Dog H-2.	1		" (20-1)				60-50-52				
		2	4 c. c. (20-1)						58-24-72			Spinal fluid, ox.
		3			1/10 gm. Ant.		60-94					No urine chart.
		4			1/1 " P.		62-90					
12-19-11	Dog I-2.	1										
		2										
		3			1/10 gm. Ant.				102-94-114			No urine chart.
		4			1/10 " P.				80-78-102			
12-19-11	Dog J-2.	1		4 c. c. (20-1)		110-114						
		2	4 c. c. (20-1)			114-110-114						Ox—Alc. precipitate.
		3	" (20-1)						114-82-124			Ox—Alc. filtrate.
		4			2/10 gm. Ant.		124-140					No urine chart.
		5			2/10 " P.		98-132					
12-20-11	Dog K-2.	1		2 c. c. (20-1)		138-130-136				—	—	
		2	2 c. c. (20-1)			128-126				—	—	Ox—Alc. ppt.
		3	" (20-1)						128-120-136	+	+	Ox—Alc. filtrate.
		4			1/20 gm. Ant.		116-140			—	+	
		5			1/20 " P.		118-144			—	+	
		6	2 c. c. (20-1)				116-140			—	++	Spinal fluid, ox.
		7		2 c. c. (20-1)						++	++	
12-27-11	Dog N-2.	1	4 c. c. (20-1)						102-80-120	+	+	" " "
		2	" (20-1)						116-54-140	+	+	" " "
		3		4 c. c. (20-1)			130-140			+	++	
		4			1/10 gm. P.				112-88-130	—	++	

PROTOCOLS—CONTINUED

Date	Case	Injections				Blood pressure effects—mm. Hg.				Urine		Remarks
		No.	Spinal fluid	Art. fluid	P. lobe	Negative	Pressor	Depressor	Dep. and pres.	Diur.	Glyco.	
12-29-11	Dog O-2.	1	4 c. c. (20-1)					140- 84-140		+	+	Spinal fluid, ox.
		2		004 Choline.				122- 84-130		+	+	
		3		001 Atropine.				118-100-124		+	+	
		4	4 c. c. (20-1)						104-56-122	−	++	" " "
		5		004 Choline.		102-104				+	++	
		6	4 c. c. (20-1)						94-50-124	+	++	" " "
		7			1/10 gm. P.			105- 60-90		−	++	
		8			1/10 " P.		100-124			−	+++	
		9			1/1- " P.		106-118			−	+++	
1-3-12	Dog P-2.	1		4 c. c. (20-1)		120-122				+	−	" " "
		2	4 c. c. (20-1)					116- 54-124		+	−	
		3		004 Choline.					112-78-122	+	−	
		4			1/10 gm. P.		106-130-98			−	+	
		5		001 Atropine.				100-88-104		−	+	
		6		4 c. c. (20-1)		84-94				−	+	
		7	4 c. c. (20-1)					96-56 96		−	+	Spinal fluid, ox.
		8		004 Choline.		102-105-102				−	++	
		9			1/10 gm. P.		94-116-100			−	++	
		10			1/10 " P.		92-108-96			−	+++	
1-9-12	Dog Q-2.	1			7 gtds. A.				148- 98-168	−	+	
		2			7 " P. I.				142-120-174	−	++	
		3			7 " P.				150-114-166	++	+++	
		4			2/10 gm. P.	136-134				+	+++	Parke Davis.
		5			2/10 " P.			128-death.		−	+++	Armour.
1-22-12	Dog R-2.	1	Ash 4 (10-1)				134-148			?	−	Spinal fluid—Perkins.
		2	4 c. c. (10-1)			134-134				+	−	" " Ginn
		3			1/10 gm. Ant.			120-68-124		−	−	
		4			1/10 " P. I.				116- 80-120	−	−	
		5			1/10 " P.			122-30-96		−	−	
		6			1/10 " P.				74- 66-104	−	−	
1-24-12	Dog S-2.	1	Ash 4 (10-1)				94-108			−	−	Ash—Perkins fluid.
		2	4 c. c. (10-1)				96-108			+	−	Spinal fluid—Perkins.
		3			1/10 gm. Ant.				110- 76-120	−	+	
		4			1/10 " P. I.				116- 94-144	−	+	
		5			1/10 " P.		116-150			−	++	
		6			1/10 " P.				124-118-134	−	+++	Armour.
1-29-12	Dog T-2.	1	Ash 4 (10-1)					152-144				Ox fluid--Ash.
		2	4 c. c. (10-1)						144- 60-156			Suppression of urine.
		3			1/10 gm. Ant.				138-130-158			
		4			1/10 " P. I.		120-156					
		5			1/10 " P.			94-68-98				
		6			1/10 " P.	96-104-98						
1-31-12	Dog U-2.	1			1/10 gm. Ant.		140-156				−	Posterior lobe removal.
		2			1/10 " P.		130-152					Suppression of urine.
		3			1/10 " P.			136-118				
2-5-12	Dog V-2.	1	Ash 4 (10-1)					144-128-152		+	−	Ox fluid—Ash.
		2	4 c. c. (10-1)					150-76 -156		+++	+	Spinal fluid, ox.
		3			1/10 gm. Ant.			138-110-144		++	+	
		4			1/10 " P. I.				130-108-150	+	++	
		5			1/10 " P.			126-88 -126		+	++	
		6			1/10 " Ant.				106- 96-126	+	+	
		7			1/10 " P.				126-104-136	−	−	No urine.
2-12-12	Dog W-2.	1	Ash 4 (10-1)						156-150-176	+	−	Ox fluid—Ash.
		2	4 c. c. (10-1)						174- 90-190	+	+	
		3			2/10 gm. Ant.				170-130-190	−	++	
		4			2/10 " P. I.				170-148-200	−	+++	
		5			2/10 " P.				172-102-186	−	+++	
		6			2/10 " P.			192-174-152		−	+++	Armour.
		7			2/10 " P.	170-176				−	+++	
4-1-12	Dog X-2.	1		Sugar sol.		124-124						No urine.
		2		" "		124-126						
		3	5 c. c. (20-1)			124-120-122						Spinal fluid, ox.
		4	" (20-1)			118-110-122						" " "
		5	" (40-1)						118-64-140			" " "
		6		Sugar sol.		118-118						
		7			2/10 gm. Ant.				106-70-120			
		8			2/10 " P. I.				104-82-120			
		9			2/10 " P.			108-40-108				
		10	5 c. c. (40-1)					108-death.				" " "
4-2-12	Dog Y-2.	1			2/10 gm. Ant.			120-84-120				No urine.
		2			2/10 " P. I.				110-80-126			
		3			2/10 " P.			112-70-104				
		4	5 c. c. (40-1)					110-36-78				Spinal fluid, ox.
4-3-12	Cat Z-2.	1			1/10 gm. Ant.			132-86-126				
		2			1/10 " P.			128-56-94				
		3			1/10 " P.			106-46-58				
5-23-12	Dog A-3.	1		Colloid.				146-106-146		−	−	
		2			1½ gtds. Ant.			152-death.		−	−	
5-23-12	Dog B-3.	1			¾ " Ant.			94-30- Adren.			+	
		2			¾ " P.		76-150					
5-24-12	Dog C-3.	1			¾ " Ant.	90-84-88						
		2			1½ " Ant.	86-80-86						
		3			1½ " P.		88-136-98					Fresh gland preparation. No urine.
		4			1½ " Whole	90-96-88						
		5			1½ " P.		88-100-80					
		6			5/10 gm. Ant.		80-92					
		7			5/10 " P.				82-62-110			

PROTOCOLS—CONTINUED

Date	Case	Injections				Blood pressure effects—mm. Hg.				Urine		Remarks
		No.	Spinal fluid	Art. fluid	P. lobe	Negative	Pressor	Depressor	Dep. and pres.	Diur.	Glyco.	
5-29-12	Dog D-3.	1	.....	.....	3/10 glds. A.	.....	.....	.....	130-80-150	.....	.....	Fresh gland preparation. Suppression of urine.
		2	.....	.....	3/10 " P.	.....	.....	.....	130-30-176	.....	.....	
		3	.....	.....	1 " P.	.....	80-196	.....	.....	.....	.....	
		4	.....	.....	1 gld. Whole	.....	126-144	.....	.....	.....	.....	
		5	.....	.....	Choroid.	.....	.....	124-98 -134	.....	.....	.....	
			.....	.....	Pineal.	.....	.....	134-116-134	.....	.....	.....	
		6	.....	.....	3/10 gld. P.	.....	130-190	.....	.....	.....	.....	
		7	.....	.....	1 " P.	.....	.....	.....	144-122-166	.....	.....	
		8	4 c. c. (8-1)	.....	.....	.....	.....	.....	156-106-170	.....	.....	Spinal fluid, ox.
		9	" (8-1)	.....	.....	.....	.....	162-116-166	.....	.....	.....	" " "
		10	.....	.....	3/10 gm. P.	.....	.....	.....	138-100-164	.....	.....	
5-31-12	Dog E-3.	1	.....	.....	3/10 gld. A.	.....	.....	146-100-144	.....	.....	.....	Post. lobe removal.
		2	.....	.....	3/10 " P.	.....	146-156-146	.....	.....	.....	.....	Fresh gland preparation. Suppression of urine.
		3	.....	.....	3/10 " W.G.	.....	.....	.....	120-100-170	.....	.....	
		4	.....	.....	3/10 " A.	.....	.....	.....	134-124-148	.....	.....	
		5	.....	.....	3/10 " P.	.....	120-170	.....	.....	.....	.....	
		6	.....	.....	3/10 " W.G.	.....	.....	.....	144-118-158	.....	.....	
		7	4 c. c. (5-1)	.....	.....	.....	.....	136-110-142	.....	.....	.....	Spinal fluid, ox.
		8	" (20-1)	.....	.....	.....	.....	126-98	.....	.....	.....	" " "
		9	.....	.....	3/10 gm. P.	.....	98-160	.....	.....	.....	.....	
		10	.....	.....	3/10 " A.	.....	.....	108-98-114	.....	.....	.....	
6-3-12	Dog F-3.	1	.....	.....	3/10 gld. A.	.....	.....	106-72-112	.....	.....	.....	Suppression of urine.
		2	.....	.....	3/10 " P.	.....	.....	.....	120-104-140	.....	.....	
		3	.....	.....	3/10 " W.G.	.....	.....	.....	110- 90-120	.....	.....	
		4	3 c. c. (20-1)	.....	.....	.....	.....	.....	88- 56-116	.....	.....	Spinal fluid, ox.
		5	.....	.....	3/10 gm. A.	.....	.....	112-80-120	.....	.....	.....	
		6	.....	.....	3/10 " P.	.....	.....	.....	106- 76-152	.....	.....	" " "
		7	3 c. c. (10-1)	.....	.....	.....	98-128	.....	.....	.....	.....	
7-12-12	Dog G-3.	1	.....	.....	1 gld. Ant.	.....	.....	.....	112- 84-138	.....	.....	Fresh preparation.
		2	.....	.....	1 " P.	.....	.....	.....	124- 32-164	.....	.....	Suppression of urine.
		3	.....	.....	1 " W. G.	.....	124-148	.....	.....	.....	.....	
		4	.....	.....	1 " P.	.....	.....	.....	124-118-170	.....	.....	
		5	.....	.....	.....	.....	.....	.....	.....	.....	.....	
		6	.....	.....	1.3 gld. P.	.....	.....	.....	114- 68-142	.....	.....	
7-16-12	Dog H-3.	1	5 c. c. (1-1)	.....	.....	.....	84-104	.....	.....	.....	.....	Spinal fluid—Truslow.
		2	2 c. c. (7-1)	.....	.....	.....	.....	98-56-70	.....	.....	.....	Spinal fluid, ox.
		3	5 c. c. (4-1)	.....	.....	74-72	.....	.....	.....	.....	.....	Fresh gland, no urine.
		4	.....	.....	1 gld. Ant.	76-80	.....	.....	.....	.....	.....	
		5	.....	.....	1 " P.	.....	86-144	.....	.....	.....	.....	
		6	.....	.....	1 " W. G.	.....	.....	.....	114- 68-142	.....	.....	
7-17-12	Dog I-3.	1	5 c. c. (1-1)	.....	.....	.....	80-116-80	.....	.....	.....	.....	Spinal fluid—Truslow.
		2	" (7-1)	.....	.....	.....	64-98	.....	.....	.....	.....	Spinal fluid, ox.
		3	" (4-1)	.....	.....	94-100	.....	.....	.....	.....	.....	Spinal fluid—Truslow.
		4	.....	.....	1 gld. Ant.	92-96	.....	.....	.....	.....	.....	Fresh gland preparation. no urine.
		5	.....	.....	1 " P.	.....	90-126	.....	.....	.....	.....	
		6	.....	.....	1 " W. G.	.....	108-122	.....	.....	.....	.....	
		7	.....	.....	1 " P.	.....	108-126	.....	.....	.....	.....	
7-26-12	Dog J-3.	1	5 c. c. (1-1)	.....	.....	82-74-86	.....	.....	.....	.....	.....	Vent. fluid—Gannon.
		2	" (1-1)	.....	.....	.....	.....	90-72-86	.....	.....	.....	Spinal fluid, ox.
		3	" (4-1)	.....	.....	84-82-90	.....	.....	.....	.....	.....	Vent. fluid—Gannon.
		4	" (20-1)	.....	.....	.....	.....	.....	88-76-98	.....	.....	Spinal fluid, ox.
		5	.....	.....	1 gld. Ant.	.....	86-96	.....	.....	.....	.....	Fresh preparation.
		6	.....	.....	1 " P.	.....	86-death.	.....	.....	.....	.....	
8-5-12	Dog K-3.	1	3 c. c. (20-1)	.....	.....	.....	.....	.....	120-94-136	+	?	Spinal fluid, ox.
		2	" (20-1)	.....	.....	.....	.....	134-110-138	.....	+	+	Spinal fluid—Waltz.
		3	.....	.....	1 gld. Ant.	.....	.....	106- 86-114	.....	+	+	Fresh preparation.
		4	.....	.....	1 " P.	.....	.....	112- 88-102	.....	+	+	
		5	.....	.....	1 " W. G.	.....	.....	.....	104-90-114	++	+	
		6	.....	.....	1 c. c. Pitu.	.....	110-120	.....	.....	+	+	
		7	.....	.....	2 " "	.....	108-120	.....	.....	+	++	
		8	.....	.....	1½ gld. P.	.....	.....	104- 82-100	.....	+	++	
8-8-12	Dog L-3.	1	5 c. c. (20-1)	.....	.....	.....	.....	94-60-102	.....	+	+	Spinal fluid, ox.
		2	" (20-1)	.....	.....	.....	.....	.....	98-84-124	++	+	Spinal fluid—Wolf.
		3	.....	.....	1 gld. Ant.	.....	.....	100-death.	.....	—	++	Fresh preparation.
8-8-12	Dog M 3.	1	5 c. c. (20-1)	.....	.....	.....	.....	.....	98-76-126	+	—	Spinal fluid, ox.
		2	" (20-1)	.....	.....	.....	.....	.....	80-48-100	++	—	Spinal fluid—Causey.
		3	.....	.....	1 gld. Ant.	.....	.....	88-death.	.....	—	—	
8-9-12	Dog N-3.	1	.....	20 c.c., Lockes	.....	78-84	.....	.....	.....	.....	.....	Vent. fluid—Levenstein.
		2	20 c. c. (1-1)	.....	.....	88-96	.....	.....	.....	.....	.....	Fresh gland.
		3	.....	.....	1 gld. P.	.....	96-140	.....	.....	.....	.....	
		4	.....	.....	1 " W. G.	.....	94-118	.....	.....	.....	.....	
		5	.....	.....	1 " Ant.	102-98-108	.....	.....	.....	.....	.....	
		6	.....	.....	1 c. c. Pitu.	.....	94-106	.....	.....	.....	.....	
		7	.....	.....	1 " "	.....	96-128	.....	.....	.....	.....	
8-9-12	Dog O-3.	1	5 c. c. (20-1)	.....	.....	.....	66-82	.....	.....	.....	.....	Spinal fluid—Glass.
		2	" (20-1)	.....	.....	.....	66-78	.....	.....	.....	.....	Spinal fluid, ox.
		3	.....	.....	1 gld. Ant.	.....	.....	76-46	.....	.....	.....	Fresh gland preparation.
		4	.....	.....	1 " P.	.....	.....	.....	52-36-68	.....	.....	
		5	.....	.....	1 " W. G.	.....	.....	68-56-64	.....	.....	.....	Fresh gland.
		6	.....	.....	1 c. c. Pitu.	68-64	.....	.....	.....	.....	.....	
		7	.....	.....	1 " "	58-62-60	.....	.....	.....	.....	.....	
		8	.....	.....	5 " "	56-56	.....	.....	.....	.....	.....	
		9	.....	.....	5 " "	56-64	.....	.....	.....	.....	.....	

parts of the gland. Record 23 shows the hæmodynamic reactions in a cat in which only depressor responses could be obtained from different portions of gland injected. That the effects of injections of cerebrospinal fluid, ox fluid and posterior lobe may be practically identical is shown by Record 24, in which we have the curves superimposed on one another. On the other hand, Records 25 to 33 show a series of unusually consistent results obtained by repeated injections of hypophyseal extract and of spinal fluid. Here there is well demonstrated (1) the depressor effect of the anterior lobe, (2) the pressor effect of the posterior lobe, (3) the neutralization of these effects in the whole gland injection, (4) the gradual diminution of pressor effects on repeated injections, (5) the depressor effect of concentrated spinal fluid. One must add also that there are many varieties of records between the extremes herein presented and that practically each one of the substances injected, at some time or other, gave marked depressor effects resulting in the death of the animal. As a rule, however, it may be stated that an animal reacting poorly for one injection responded also poorly to the other substances and that the few animals under chloretone reacted less decisively than those under ether.

A statistical study of some 305 injections and tracings is given in Table 2, furnishing the opportunity of a more quanti-

TABLE 2.—SUMMARY OF HÆMODYNAMIC EFFECTS OF INJECTIONS OF EXTRACTS

	No.	Negative	Depressor	Pressor	Depressor and pressor	Combined dep.-pres. average
Spinal fluid.....	120	15—12.5%	30—25 % av.—40 mm. 5 deaths.	25—20.9 % av.—17 mm.	50—40 % 25—19 mm.	30—18 mm.
Art. spl. fluid....	29	17—59. %	6—20.7 % av.—16 mm. 1 death.	1—3.4 % av.—10 mm.	5—17 % 16—18 mm.	16—18 mm.
P. lobe	102	3— 2.9%	19—18.6 % av.—32 mm. 3 deaths.	46—45 % av.=33 mm.	34—33.3 % 26—25 mm.	28—34 mm.
Ant. lobe.....	36	5—14. %	14—39 % av.—34 mm. 4 deaths.	6—16.6 % av.- 14 mm.	11—30.6 % 28—18 mm.	31—18 mm.
Para-intermedia.	8	0	0	1—12 % av.—30 mm.	7—88 % 23—22	23—23 mm.
Whole gland.....	11	0	1—9 % av.—13 mm.	4—33 % av.—16.	6—55 % 19—18.4	18—17 mm.

tative study of these qualitative reactions done under uniform conditions.

Quantitatively, the averages of the combined pressor effect of spinal and artificial fluid are about the same, while the depressor effect of the spinal fluid is about twice that of artificial fluid; on the other hand the posterior lobe injection while accompanied by a depressor effect of short duration, is essentially a pressor effect both from the height of blood pressure curve and from the duration of the same. Just how much of the pressor effect of the depressor-pressor sequence of spinal and artificial fluid is due to the over-reaction of the animal to the primary depressor effect is difficult to state, but the fact that it is constant when occurring alone and in the sequence, in both fluids, seems to indicate that it most probably is associated with the inorganic content of these fluids and not due to any definite, specific, blood pressure raising entity. This latter statement is confirmed by the disappearance of the marked depressor effect on injection of the ash from an equal bulk of concentrated fluid; this is seen graphically in Records 34-35. These data seem to indicate that the predominating hæmodynamic substance in concentrated spinal fluid is a depressor one rather than a pressor one as would be indicated by the presence of a posterior lobe secretion.

4. *Diuretic Effects.*—A study of the diuretic effects of the injections is given in Table 3.

TABLE 3.—SUMMARY OF URINARY EFFECTS OF INJECTION OF EXTRACTS

	Diuresis			Glycosuria		
	No.	Positive	Per cent	No.	Positive	Per cent
Spinal fluid.....	83	57	79	95	44	46
Art. spl. fluid.....	21	15	71	28	13	46
P. lobe	71	15	21	69	59	86

A definite diuresis occurs after most of the injections of spinal and artificial fluid. This is due most probably to the hypertonicity of the solution injected. With the posterior

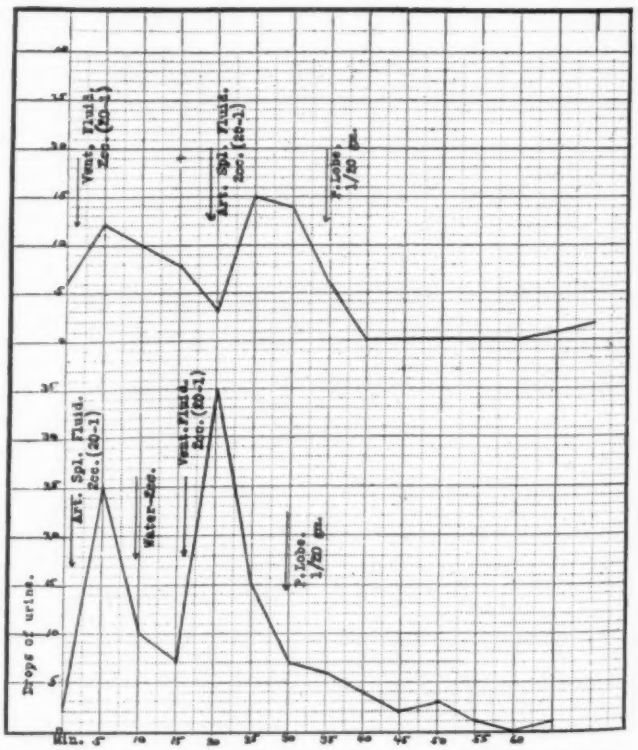


CHART I.—Showing diuretic effects of spinal fluids and antidiuretic effects of the posterior lobe extract in dogs.

lobe injection, however, the slight transient diuresis which may occur is usually followed by a definite decrease in the urinary outflow which persists for a longer time so that, concentrated solutions injected subsequently are unaccompanied

by the usual diuretic effect. This anti-diuretic effect is quite marked and is contrary to the observations of Herring[8] regarding the diuretic effects of the posterior lobe and seem to confirm those recently made by Motzfeldt,[9] who found a definite decrease in the urinary outflow as a sequence to posterior lobe injections. Chart I shows the anti-diuretic effects of posterior lobe injections in contrast to the diuretic effect of concentrated cerebrospinal and artificial fluids.

5. *Glycogenic Effect.*—A study of the production of glycosuria from the above injections is also given in Table 3. Exact observations of this reaction were accompanied by considerable difficulty owing to the fact that the first appearance of sugar in the urine invalidated to a certain extent the correctness of interpreting the results of subsequent injections. However, by making tests of a quantitative nature some definite conclusion could be obtained. It is well to note that the glycosuria was produced to about the same percentage of frequency in both spinal and artificial injections, while the posterior lobe injection was almost invariably followed by a glycosuria or increase in urinary sugar contents. The production of glycosuria under such conditions occurred more readily in rabbits than in dogs.

SUMMARY

From the aforegoing data it is evident that:

1. Concentrated cerebrospinal fluid, human and bovine, when injected intravenously into rabbits and dogs is accompanied by a depressor-pressor sequence similar to that produced by equal concentrates of "artificial spinal fluid," a solution isotonic to normal spinal fluid. The small pressor component is quantitatively equal to that of the isotonic solution and is due probably to the over-reaction of the animal to the depressor effect of the concentrated inorganic sodium and potassium salts. The augmented depressor effect of the cerebrospinal fluid is due to the presence of a small amount of organic material in solution, making the effect essentially a depressor one instead of a pressor one indicative of the posterior lobe secretion.

2. Diuresis usually accompanied the injection of concentrated spinal and artificial fluid and is due most probably to hypertonicity of the salt solution. Injections of the posterior lobe extract were usually followed by an anti-diuretic effect, leading to suppression of urine in a large number of cases.

3. Glycosuria follows the injection of concentrated spinal and artificial fluid in about the same number of cases and is most probably associated with the high concentration of the inorganic salts. It is more common as a sequence to injections of posterior lobe extract and is usually greater in amount. This glycosuric effect is seen more frequently in rabbits than in dogs.

NATURE OF DEPRESSOR SUBSTANCE

Schaefer and Oliver in their pioneer researches upon the gland attributed the hæmodynamic effect to the whole gland. Howell[10] in 1898 showed that this property was characteristic of the posterior lobe and this finding was confirmed by Schaefer and Vincent,[11] in 1899, who demonstrated an active depressor substance soluble in alcohol and a pressor substance in soluble in that reagent. Hamburger[12] in 1904 demonstrated the existence of a depressor and a pressor substance in the anterior lobe, but Schaefer and Herring[13] in 1906 failed to corroborate these findings. Cyon,[14] in 1907, investigated the depressor substance of the posterior lobe and thought that it might be similar to choline. Hamburger,[15] in 1910, repeated his work of 1904, getting identical results as previously, and questioned the method of preparation used by Schaefer and Herring. Lewis,[5] in 1911, found that the pars intermedia and nervosa have definite pressor effects and the pars anterior contained a depressor effect and a small pressor effect, the latter due most probably to its intimate contact with the intermedia. It was his opinion that the secretion was produced in the pars intermedia and given to the pars nervosa. In 1912, Engeland and Kutscher[16] drew attention to a substance obtained from the whole gland preparation which had the marked property of stimulating smooth muscle but had no effect upon the blood pressure. Herring,[17] in 1915, found no pressor substance in either anterior lobe or pars intermedia, but a definite pressor substance in the posterior lobe. He considered the substance discovered by Engeland and Kutscher to represent only one of the stages in the formation of the pressor secretion which was formed in the pars intermedia and given to the pars nervosa, undergoing changes there as characterized by changes in the hyaline bodies. There thus is seen to be marked confusion regarding the pressor and depressor effects of the various parts of the pituitary gland. This most probably is due to the fact that it is very difficult to make an absolute separation of the different structures of the gland and also because of the variability of the responses in the animal itself, as seen from the preceding records.

Examination of records of injection of concentrated cerebrospinal fluid, anterior and posterior lobes, pars intermedia and whole gland usually show a primary depressor effect followed by a pressor response of greater or less extent depending upon the part of the gland injected. The similarity of this depressor response is very striking and leads one to infer a common cause or origin for it. A quite similar depressor curve is also seen in tracings of injections of colloid material taken from the interlobar cleft and also from extracts of choroid plexus and pineal gland, as can be seen in Records 36-37.

Several definite conclusions are reached regarding this depressor substance.

1. *It is Common to All the Above-Named Extracts and Fluids.*—In spite of the greatest care used in separating the different parts of the pituitary gland, injections of these separated substances almost invariably give a depressor effect either as the whole or part of the reaction.

2. *Nature of Depressor Effect.*—This occurs as a marked vaso-dilator effect with marked fall in blood pressure. It is usually in the form of a primary fall and followed by a greater or less pressor effect. Depressor effect is usually of short duration. Injections showing pressor and depressor effects alone are rather unusual, the depressor and pressor sequence being

the usual reaction. The pressor effect is most marked in the posterior lobe and pars intermedia, whereas the depressor effect is most marked in the concentrated spinal fluid, human and bovine, and in the anterior lobe. Death from extreme depressor effects is noted in about 13 out of 305 injections. It followed injections of concentrated spinal fluid, anterior and posterior lobe, occurring often from a primary injection and also as a sequence to subsequent injections. In several cases death of the animal from continued depressor effect was prevented by the injection of adrenalin which caused a marked vaso-constrictor effect with rise in blood pressure and resumption of animal function. Records 38-39 indicate the depressor effect leading to a fatal outcome and one in which death was most probably prevented by the injection of adrenalin.

3. *Effect on Smooth Muscle.*—Several observations show that these substances have a definite stimulating effect on smooth muscle such as intestine, bladder and uterus. The uterus in several instances emptied itself of the fœtus after injection of these extracts and eviscerated animals showed a moderate increase of peristalsis on injection.

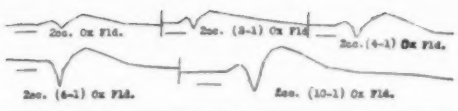
4. *Solubility.*—This depressor substance evidently is soluble in water and in alcohol. Solutions of the evaporated alcoholic filtrates of both spinal fluid and posterior lobe, when injected into an animal, showed the identical depressor effect characteristic of concentrated spinal fluid and posterior lobe injections, while solutions of the alcoholic precipitate gave no appreciable effect in case of the spinal fluid and only a pressor effect on posterior lobe injections (See Records 40-41).

5. *Depressor Substance Not Choline.*—Choline is a substance produced in the decomposition or destruction of cell life and is physiologically demonstrated by showing a marked depressor effect when introduced into the body, a depressor effect which can be abolished by atropine. Records 42-47 demonstrate clearly the persistence of the depressor effect of the concentrated cerebrospinal fluid injections before and after the administration of atropine and the obliteration of the choline depressor effect after that injection.

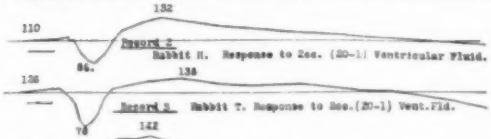
6. *Not Affected by Stimulation of the Gland.*—Weed, Cushing and Jacobson,[18] in 1913, demonstrated that glycosuria could be produced in animals with available glycogen by (1) direct stimulation of the hypophysis and (2) by stimulation of the superior cervical ganglion after the exclusion of all cephalad impulses; thus indicating the liberation of some substance, presumably of hypophyseal origin, causing glycogenolysis and glycosuria. Rabens and Lifschutz[19] in 1915, however, by using similar methods failed to get any evidence of an increase in the reducing power of the blood, as an index of such reaction, but in 1915 Keeton and Becht[20] and also Shamoff[21] in the same year, obtained glycosuria and an increase in the reducing power of the blood by a similar procedure and thus confirmed the original observations in that particular. If such stimulation increased the secretory activity of the gland, it seemed quite probable also that some additional hæmodynamic reaction should result from the outpouring of the secretion either into the blood-stream or into the cerebrospinal fluid. Stimulation of the hypophysis directly and of the isolated superior cervical ganglion gave the usual glycosuria but failed to show any special pressor or depressor effect except that which accompanied the manipulation of the gland, itself (See Records 48-49).

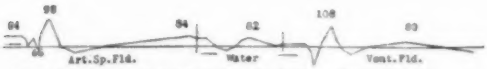
7. *Relation to Hypophysectomy.*—Ductless glands are generally supposed to elaborate some special substance or internal secretion necessary for the body economy and the conditions designated as hypo-activity and hyper-activity to be accompanied by essentially characteristic changes in the animal and in their reactions to the special specific substance involved. Consequently, it was thought advisable to see what special or altered effects the injections of concentrated spinal fluid, anterior and posterior lobe extracts, would have upon a "hypo" condition experimentally produced. Injections of cerebrospinal fluid, anterior and posterior lobe extracts, gave in hypophysectomized animals reactions not essentially different from those of normal animals nor did they elicit any suggestion of any special hypo- or hyper-sensitivity to the specific substance involved by the anterior or posterior lobe removal.

That tissue extracts on injection have hæmodynamic power had been recognized many years ago; by Schaefer and Moore[22] in 1900 and again by Halliburton[24] in 1901, these two latter investigators differing as to whether it was a choline effect. In 1903 Vincent and Sheen[25] showed that typical depressor curves could be obtained from a variety of tissue extracts and concluded that all glandular structures and probably all animal tissue contained, in their extracts, a depressor and pressor substance. Since then similar effects have been demonstrated by many investigators. Since the discovery of Enriguez and Hallion,[26] in 1904, that a stimulant to intestinal musculature could be obtained from extracts of gastric and intestinal mucosa, there arose a group of substances descriptively named "peristaltic hormones" and "motilines," substances obtained from extracts of various tissues and exhibiting the symptom-complex of stimulating smooth muscle and at the same time having a marked depressor effect on blood pressure. The characteristic "peptone shock" of Witte's peptone and the depressor effect of *secretin* were such typical substances. Popielski,[27] in 1909, working on this depressor substance of peptone showed that its effect was not due to choline, which some time previously in 1908 had been identified by Lohman and Von Furth[28] and by Schwartz and Von Furth[29] as one of the depressor substances in tissue extract. He gave the name of "vaso-dilatin" to this hypothetical substance and also concluded that it was identical with the *secretin* of Bayliss and Starling.[30] In 1910 Dale and Laidlow[31] in describing the action of histamine-B. iminazolylethylamine showed the similarity of its reaction to those of peptone, the "vaso-dilatin" of Popielski and to "histamine-like" substances in other tissue extracts. Barger and Dale in 1911[32] isolated the depressor substance from intestinal mucosa and concluded it to be histamine and that the "vaso-dilatin" of Popielski contained this same substance. In 1917 Abel and Pincoff[33] in working with some albumoses in pituitary extract, prepared from intestinal mucosa a water-soluble

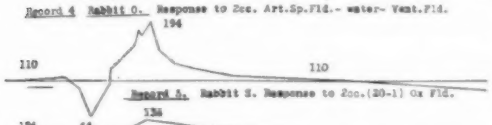


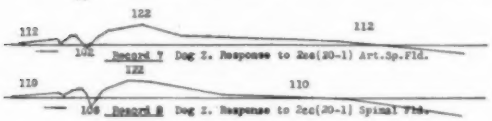
Record 1 Rabbit C. Response to increasing concentrations of Ox Spinal Fluid.

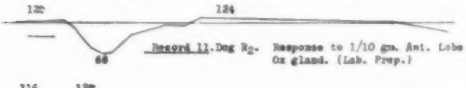




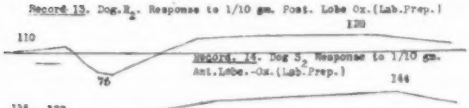
Record 4 Rabbit O. Response to Zoc. Art.Sp.Fld.- water- Vent.Fld.

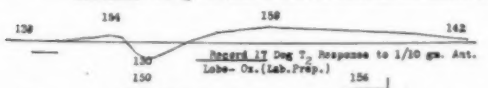


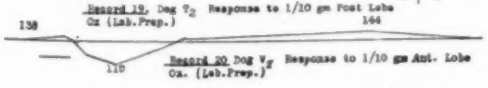


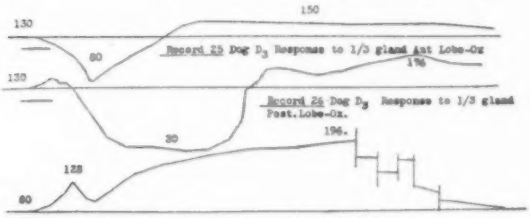


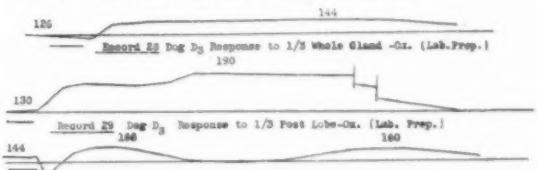
Record 13. Dog.R2. Response to 1/10 gm. Post. Lobe Ox.(Lab.Prep.)

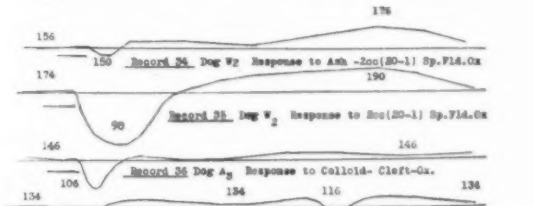


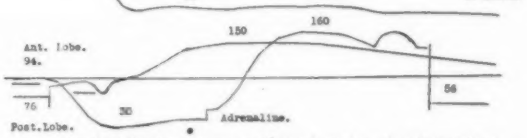


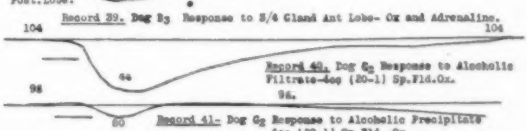


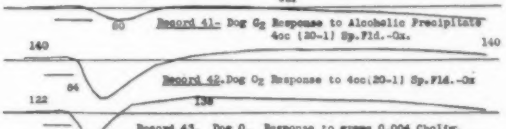


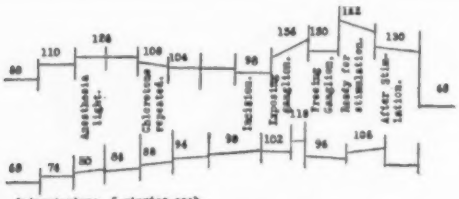




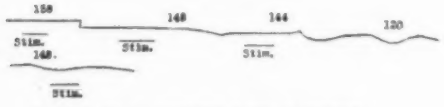








Record 40 Dog C_4 Stimulation-faradic-Of the isolated Superior Cervical Ganglion.



Record 42 Cat 2_2 Stimulation-faradic-of Hypophysis.

substance indistinguishable in its effects from posterior lobe of the pituitary gland and inferred the presence of albumoses in both substances. They were led to infer that the motiline substance in the posterior lobe is not a hormone specific to the gland but a substance found in many other tissues, having its origin either in the tissues of the cell itself or as a product of its activity. Finally, in 1919, Abel and Kubota [28] isolated the active principal histamine from pituitary glands, intestinal mucosa, liver, muscle, peptone and other substances showing that it occurs widely in tissues and that the so-called "motiline," "peristaltic hormone," "vaso-dilatin," "histamine-like" substances, the plain muscle stimulant and blood depressor substance, were all identical and due to the specific substance "histamine."

Cerebrospinal fluid from its dual origin either from the choroid plexus as a specific secretion or selective filtrate, and as a source of drainage for the peri-vascular nerve spaces contains a small amount of organic matter in solution. Its properties and physiological reactions when injected intravenously as a concentrate are identical with those obtained from the various tissue extracts in general and with the depressor substance of the pituitary gland in particular; reactions now definitely demonstrated to be due to the active principal histamine which has been definitely isolated from these very tissues, histamine, an organic base, a product of the hydrolytic cleavage or decomposition of the protein molecule, most probably found in all animal tissues and secretions either as a part of the cell itself or incident to cell activity. The physiological reactions of the spinal fluid, a depressor effect, seem to be due to the depressor substance histamine and not to any specific secretion of the pituitary gland as was formerly contended.

Conclusions

1. Cerebrospinal fluid from human and bovine sources in concentration gives physiological reactions identical with those obtained from the injection of various tissue extracts, effects most probably due to the presence of histamine.

2. There is no definite evidence of the presence of a pressor substance in the cerebrospinal fluid suggestive of any posterior lobe secretion. It seems rather improbable that the pituitary gland gives its secretion into the ventricles or into the cerebrospinal fluid.

3. All pituitary gland extracts show marked variability as far as their responses are concerned on intravenous injection. They all show a depressor effect common to the tissue extract. In general it may be said:

(a) Anterior lobe exhibits depressor effect mainly.

(b) Posterior lobe a moderate depressor followed by a specific pressor effect.

(c) Pars intermedia has a small depressor, followed by a pressor effect.

(d) Whole gland shows a neutralization of the depressor and pressor effects.

(e) The posterior lobe secretion, if it is a specific secretion, is most probably produced in the pars intermedia and finds its way into the pars nervosa.

4. The posterior lobe extract on intravenous injections appears to have an antidiuretic rather than a diuretic effect.

5. Glycosuria is produced by intravenous injection of posterior lobe extract in a number of cases. This glycogenic effect is more marked in the rabbit.

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BIOGRAPHY OF SIR WILLIAM OSLER

Lady Osler has requested me to prepare a biography of her husband, and I will be most grateful to anyone who chances to see this note, for any letters or personal reminiscences, or for information concerning others who may possibly supply letters.

Copies of all letters, no matter how brief, are requested, and if dates are omitted it is hoped that they may be supplied if possible.

If the originals are forwarded for copy they will be promptly returned.

HARVEY CUSHING, M. D.,
Peter Bent Brigham Hospital,
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EXPERIMENTAL OBSERVATIONS UPON THE URETERS, WITH ESPECIAL REFERENCE TO PERISTALSIS AND ANTIPERISTALSIS

By G. B. WISLOCKI,
Arthur Tracy Cabot Fellow, Harvard Medical School,
AND
V. J. O'CONOR,
Assistant Resident Surgeon, Peter Bent Brigham Hospital, Boston
(From the Laboratory of Surgical Research, Harvard Medical School)

The peristaltic movements of the ureters have been the object of repeated study. Thus Engelmann[1] in 1869 first described in detail the nature of the peristaltic contractions occurring in the living ureter. He observed that the contractions normally originate at the renal pelvis and proceed toward the bladder. He recorded the frequency of the peristaltic waves and the rate at which they travel. He also noted that the movements of the ureters are independent of one another. Finally, he watched the response of the ureteral musculature to mechanical and faradic stimulation and decided from these experiments that the contractions he had seen were independent of any intrinsic or extrinsic nerves, and that the impulse to contract was conveyed directly from one muscle cell to another.

A further advance in our knowledge of the physiology of the ureter was made in 1881 by Sokoloff and Luchsinger.[2] They passed physiological salt solution through the ureter under varying pressures and noted the effect upon peristalsis. They observed that the greater the pressure of the fluid passing through the lumen of the ureter the more frequent and vigorous the peristaltic waves became.

Protopowpow[3] in 1897 investigated the finer structure of the ureter and demonstrated rich nerve plexuses and numerous ganglia in its wall. He showed that stimulation of the

splanchnic nerve causes increased ureteral peristalsis, whereas section of the the same nerve inhibits peristalsis. He also observed that drugs are capable of stimulating or inhibiting the contractions of the ureteral musculature; thus, he noted that atropin first increases and then inhibits peristalsis.

In recent years the contractions of the ureter have been studied very carefully by the graphic method. Some investigators have obtained tracings of the movements of the ureter *in situ* while others have suspended rings or strips of excised musculature in warm, oxygenated Ringer's or Locke's solution. In this way Lucas,[4] Macht[5] and Satani[6] have graphically illustrated normal ureteral contractions and the effect of various drugs on them. They have been able to demonstrate that the ureter possesses, like other smooth muscle, sympathetic and autonomic nerve fibres which respond in a characteristic way to pharmacologic agents.

Satani,[7] in a recent paper, discusses the causes of ureteral contractions. He believes that the peristalsis of the ureter should be referred to several factors which act in cooperation. The most important of these are reflex stimulation of the motor nerves, direct mechanical distention of the ureteral musculature and a local reflex which is stimulated by the salts contained in the urine.

The object of our investigations has been to study the behavior of the ureter in the living animal under various experimental conditions. We have investigated primarily the peristaltic activity of the ureter after complete and partial ligation and, secondarily, the behavior of the ureter during the passage of glass beads from the renal pelvis to the bladder. The similarity between these experimental conditions and those encountered clinically in hydronephrosis and from ureteral calculi lend additional interest to the observations.

We have also repeated some experiments made by previous observers on regurgitation of fluid through the uretero-vesical orifice to determine what rôle peristalsis and antiperistalsis play in this phenomenon. Finally, we have made a few notes on the behavior of the ureter during experimental ureteral catheterization.

The results of our experiments may best be presented under the following headings:

1. The effect on peristalsis of partial and complete ligation of the ureter.

2. The behavior of the ureter during the passage of glass beads of various sizes.

3. The activity of the ureter during regurgitation of fluid from the bladder.

4. The behavior of the ureter during ureteral catheterization.

1. The Effect on Peristalsis of Partial and Complete Ligation of the Ureter

Eight dogs and eleven rabbits were employed in these experiments. Of the dogs, three had one ureter completely ligated, five had one ureter partially so. In the rabbits, the ureter was completely ligated in nine, and partially ligated in two animals.

The experiments consisted in operating on the animals under aseptic conditions, placing a partial or complete ligation about one ureter, preferably the left, allowing the animal to recover, and subsequently, after a period of days, weeks or months, opening the animal's abdomen and observing the peristaltic movements. Black silk thread was used when we tied off the ureter completely. For the partial ligation a narrow rubber band (2 mm. wide) was secured about the ureter so as partially to compress its lumen.

The results of these experiments can best be described by presenting some of the protocols in detail. In order to prevent needless repetition, however, no more protocols than necessary will be given and a brief summary at the end will incorporate the essential observations of all the experiments.

The following protocols illustrate the results of partial ligation:

Rabbit 19.—Male. Nov. 5, 1919. Partial ligation of the left ureter at the junction of its upper and middle thirds.

Dec. 9, 1919. A laparotomy under ether anæsthesia is performed. The left ureter is found moderately dilated above the rubber band. Below the band the ureter appears normal. The dilated portion of the ureter exhibits very active peristaltic movements. No spontaneous antiperistaltic waves are noted but on pinching the dilated ureter just above the band vigorous reversed peristaltic waves are elicited which pass from the point of stimulation up the ureter and disappear into the renal pelvis. On cutting through the dilated ureteral wall its musculature is found much thickened. A segment of the wall placed in warm, oxygenated Locke's solution contracts vigorously. The portion of the ureter below the band contracts with normal frequency and independently of the dilated ureter above. The opposite ureter shows contractions of normal rate and frequency.

Dog 3.—Female. Nov. 12, 1919. Left ureter partially ligated midway between the renal pelvis and the bladder.

Jan. 23, 1920. A laparotomy under ether is performed. The upper part of the left ureter is markedly dilated, the portion below the ligature appears normal. Vigorous peristaltic and antiperistaltic waves are observed in the dilated ureter. There are from 4 to 6 waves per second. The peristaltic waves originate in the renal pelvis, and travel down the dilated ureter to the rubber band where most of them cease. A few, however, pass the constriction and proceed in a normal manner toward the bladder. The peristaltic movements are frequently interrupted by one or more reversed peristaltic waves which originate at the rubber band and travel upwards to the renal pelvis. On section the musculature of the ureter is found tremendously hypertrophied. Strips of the hypertrophied wall contract readily in warm, oxygenated Locke's solution.

Dog 5.—Male. Nov. 14, 1919. Left ureter partially ligated 6 cm. above the bladder.

Feb. 9, 1920. A laparotomy under ether is performed. A well-marked hydroureter and hydronephrosis are encountered. Vigorous but rather infrequent peristaltic contractions of the ureter are observed with now and then a wave in the reverse direction. After aspiration of part of the fluid contained in the dilated ureter the contractions become more frequent and vigorous. On application of a crystal of barium chloride to the surface of the ureter a constriction ring is formed from which peristaltic waves proceed in both directions at regular intervals. The movements of the opposite ureter are normal.

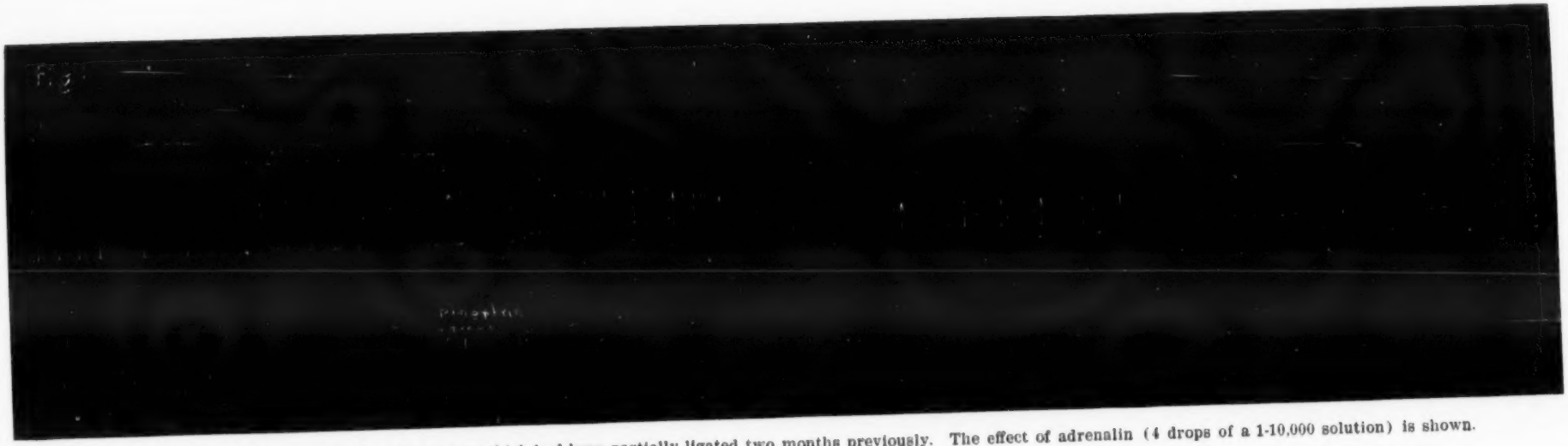

FIG. 1.—Tracing of the contractions of a ureter which had been partially ligated two months previously. The effect of adrenalin (4 drops of a 1-10,000 solution) is shown.

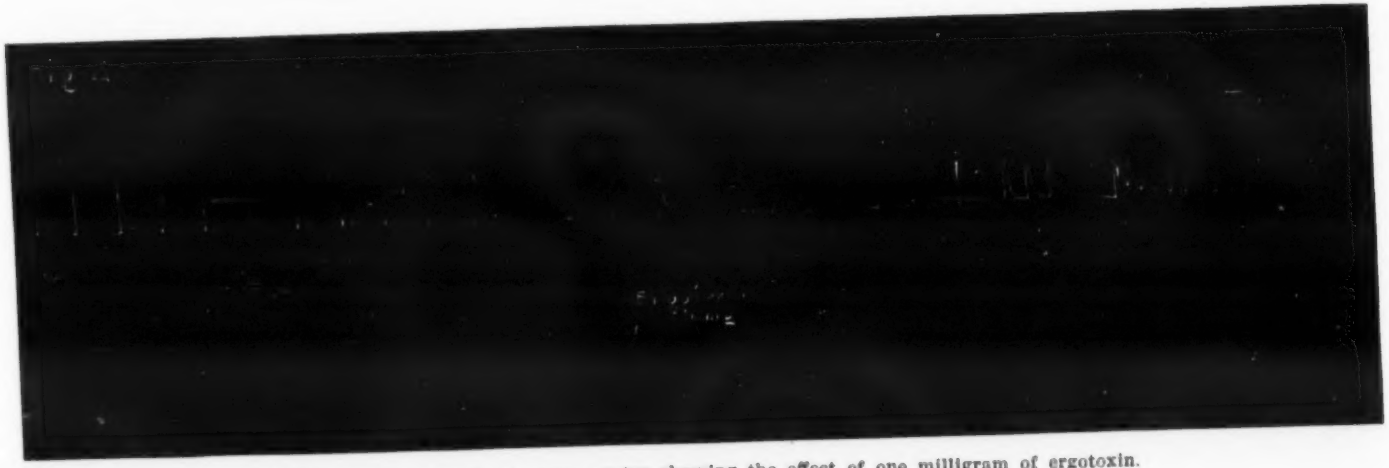

FIG. 2.—Tracing from the same ureter showing the effect of one milligram of ergotoxin.

The following protocols illustrate the effect of complete occlusion of the ureter:

RABBIT 21.—Female. Nov. 5, 1919. Complete ligation of the left ureter in its middle with silk tie.

Nov. 17, 1919. A laparotomy is performed under ether. The left kidney and ureter are found markedly distended with fluid. No peristaltic movements are visible in the dilated ureter. Below the tie the ureter, which appears normal, is quiescent but contracts on stimulation. Peristaltic waves cannot be elicited by pinching the dilated ureter or applying a crystal of barium chloride to its surface. The barium chloride produces, however, a visible muscular constriction at the point of application. After the aspiration of about 10 c. c. of fluid from the ureter its musculature immediately commences to contract violently. Contraction waves are observed passing in both directions. On section the musculature is found to be greatly hypertrophied. The behavior of the ureter on the opposite side is normal.

DOG 6.—Male. Nov. 18, 1919. Complete ligation of the left ureter with silk thread about 8 cm. from the bladder.

Feb. 9, 1920. A laparotomy is performed under ether. An enormously dilated ureter and kidney are encountered. No peristaltic movements are visible in the dilated ureter nor can any be elicited on pinching the musculature. About one-half of the fluid contained in the ureter and kidney is aspirated whereupon peristaltic and anti-peristaltic contractions ensue of such violence and so frequently that the ureter appears to be performing vermiform movements. On refilling the ureter with salt solution these movements are brought to a standstill, to commence once more when the internal pressure is again relieved. On section the musculature of the ureter is found tremendously hypertrophied. Suspended in warm, oxygenated Locke's solution, rings of the musculature contract spontaneously. The ureter on the opposite side exhibits normal peristalsis.

SUMMARY

The results of these experiments upon partially and completely ligated ureters may be summarized as follows:

After partial ligation of the ureter its lumen increases in diameter and its musculature hypertrophies. When an incompletely ligated ureter is examined several weeks or months after operation, spontaneous peristalsis and frequently antiperistalsis is encountered. The peristaltic waves are always more vigorous and occasionally more frequent than those seen in the normal ureter. Vigorous antiperistaltic waves, if not spontaneously present, may be elicited by pinching. By the application of a crystal of barium chloride to the surface of the dilated ureter a constriction ring is formed from which peristaltic waves proceed in both directions. The ureter below the partial ligature exhibits normal spontaneous peristaltic contractions.

The lumen of the completely ligated ureter is somewhat larger than that of the partially ligated one. The musculature is also hypertrophied. The completely ligated ureter seldom shows any spontaneous peristaltic movements nor does it usually react to stimuli. When, however, part of the contained fluid is released, violent peristaltic and antiperistaltic movements commence, which are in no way distinguishable from those observed in the partially ligated ureter.

Bands of muscle from both partially and completely ligated ureters contract vigorously when suspended in warm, oxygenated Locke's solution. The action of drugs on these preparations can be readily studied.

Figs. 1 and 2 show the effect of adrenalin and ergotoxin upon excised rings of musculature from a hydroureter.

2. THE BEHAVIOR OF THE URETER DURING THE PASSAGE OF GLASS BEADS

In these experiments four rabbits and nine dogs were used. Somewhat flattened and perforated glass beads were introduced aseptically into the pelvis of the left kidney through a small nephrotomy puncture wound. After a few days or weeks had elapsed the animal was again anæsthetized, a laparotomy was performed and the behavior of the ureter observed. Beads of different sizes were employed ranging in diameter from 0.08 up to 0.25 inch (2-6 mm.).

The following protocols, arranged with reference to the increasing size of the beads used, describe our observations:

DOG 7.—Male. Dec. 2, 1919. Left lumbar incision. Introduction of 6 perforated glass beads having a mean diameter of 0.085 inch (slightly less than 2 mm.) into the left renal pelvis.

Dec. 8, 1919. A laparotomy is performed under ether. The left ureter appears normal in shape and circumference. Unusually vigorous peristaltic waves are seen travelling down the left ureter, about two per minute. A bead is visible in the lumen of the ureter about one-third of the way from the renal pelvis to the bladder. The bead does not interfere with the passage of the peristaltic waves, nor is the ureter dilated above it. On opening the renal pelvis only one bead is found remaining there. The mucosa and musculature of the pelvis and ureter appear normal. None of the beads which have been passed are found in the bladder.

DOG 8.—Male. Dec. 16, 1919. Left lumbar incision. Introduction of 8 perforated glass beads into the left renal pelvis. The mean diameter of the beads is 0.085 inch (slightly less than 2 mm.).

Dec. 23, 1919. A laparotomy is performed under ether. The left ureter is hypertrophied in its entire length and the lumen is slightly dilated. Normal peristaltic waves are observed passing down the ureter at regular intervals. No beads are found in the lumen of the ureter and on opening the kidney none are located in the renal pelvis. The uretero-vesical orifice appears to be functioning normally. The right ureter shows nothing unusual.

DOG 9.—Female. Dec. 29, 1919. Left lumbar incision. Introduction of six perforated glass beads into the left kidney pelvis. The mean diameter of these beads is 0.1 inch (approximately 3 mm.).

Jan. 8, 1920. A laparotomy is performed under ether anæsthesia. The lower part of the ureter is not dilated or hypertrophied and normal peristaltic waves traverse it at regular intervals. A bead is discovered in the lumen of the ureter about 2 cm. below the renal pelvis. The ureter above the bead is slightly dilated. The bead does not interfere with the passage of the peristaltic waves. On opening the kidney three beads are found free in the tips of the calyces. One other bead is found in the bladder.

DOG 10.—Male. Jan. 2, 1920. Left lumbar incision. Introduction of eight perforated glass beads into the left kidney pelvis. The mean diameter of these beads is 0.1 inch (approximately 3 mm.).

Jan. 15, 1920. A laparotomy is performed under ether. The left ureter exhibits regular vigorous peristaltic contractions. No beads are discovered in the ureter or renal pelvis.

Dog 11.—Male. Jan. 6, 1920. Left lumbar incision. Introduction of five perforated glass beads into the pelvis. The mean diameter of these beads is 0.16 inch (approximately 4 mm.).

Jan. 13, 1920. A laparotomy is performed under ether anæsthesia. Two beads are observed in the left ureter about one-third of the way between the renal pelvis and the bladder. These beads appear partially to occlude the ureter because there is a marked degree of hydronephrosis. Strong peristaltic waves, at regular intervals, are observed commencing just below the lowest bead and sweeping down to the bladder. The ureter above the beads exhibits feeble peristalsis. Part of the fluid distending the ureter is aspirated but even then the peristaltic contractions do not become stronger. The waves commence at the renal pelvis but stop at the first bead. Peristalsis below is independent of that above the beads. The opposite ureter behaves normally.

Dog 13.—Male. Jan. 9, 1920. Left lumbar incision. Introduction of seven beads into the left renal pelvis. These beads vary in size within limits of 0.20 to 0.25 inch (5-6 mm.).

Feb. 10, 1920. A laparotomy is performed under ether anæsthesia. The left ureter appears slightly dilated and its musculature somewhat thickened. Three beads are found lodged in the lumen of the ureter. The lowermost of them is lodged in the intramural portion. The ureter appears uniformly dilated from this point upwards. About 4 cm. above the first bead a second smaller one is located and about equidistant above this one a third and somewhat larger one. Vigorous peristaltic waves are observed starting at the renal pelvis and descending the ureter to the first obstruction, where they cease. New peristaltic waves are seen to arise immediately below the uppermost bead and proceed toward the bladder. These waves are not interrupted in their course by the second somewhat smaller bead which is rocked to and fro as the contractions sweep by it. No spontaneous antiperistaltic movements of the ureter are observed arising in the neighborhood of any of the beads. On gently pinching the ureter, however, above a bead an antiperistaltic wave is readily elicited. The remaining beads are found in the calyces of the renal pelvis. The mucosa of the pelvis and ureter appears normal. The opposite ureter behaves normally.

SUMMARY

The behavior of perforated beads may be summarized as follows:

Beads of small caliber are propelled down the dog's ureter without any difficulty by a series of peristaltic waves and are finally expelled into the bladder. They leave no trace of their former presence in the ureter. Beads of somewhat larger diameter require a longer period to traverse the ureter. They stimulate the ureteral musculature to prolonged peristaltic exertion before they are expelled. Neither a bead of this nor the preceding size obstructs the passage of peristaltic waves from pelvis to bladder. As a result of the passage of several such beads the ureteral wall may become slightly hypertrophied.

Finally beads have been employed which become lodged in the lumen of the ureter, most commonly near the renal pelvis or in the intramural segment. These cause moderate dilatation and hypertrophy of the ureteral wall above the point of obstruction. Vigorous peristaltic waves come down the hypertrophied ureter from the renal pelvis but invariably stop at the bead. Below the bead other peristaltic waves originate and proceed toward the bladder. Antiperistaltic waves have not been observed arising spontaneously at the point of obstruction although they may be readily called forth by gently pinching the ureter just above the bead.

3. The Behavior of the Ureter During Regurgitation of Fluid from the Bladder

Semblinoff,[8] in 1883, and Lewin and Goldschmidt,[9] in 1893, observed that when they injected a colored solution under moderate pressure into the bladder of an anæsthetized rabbit the bladder contents regurgitated in many instances into one or both ureters. The latter investigators made the observation that the bladder wall must possess a good degree of tone and be only moderately distended for the experiment to succeed. They also noted that the phenomenon rarely occurred unless peristalsis was visible in the ureters and in many instances they claim to have observed an antiperistaltic wave in the ureter at the moment that regurgitation took place.

Courtade and Guyon[10] repeated Lewin and Goldschmidt's experiments. They were able to produce regurgitation in 20 out of 32 rabbits but in only 5 out of 25 dogs.

Marcus[11] succeeded repeatedly in producing regurgitation in rabbits. He believes that a reversed peristaltic wave is nearly always responsible for the reflux.

On the other hand, Sampson[12] in a series of nearly 20 dogs was unable to produce a reflux of fluid from the bladder into the normal ureter.

Young[13] states that in two cadavers he was unable to force fluid into the ureters by hydraulic pressure. Satani[9] reports that regurgitation of fluid never occurs in the excised bladder and ureter of the pig. He concludes from his experiments that the prevention of a reflux from the bladder into the ureter is complete under normal conditions.

Kretschmer[14] claims to have observed by the use of radiograms on the human subject that solutions of thorium, collargol or cargentos occasionally find their way from the bladder into the renal pelvis by regurgitation. He ascribes both this phenomenon and the so-called retrograde movement of some renal calculi to antiperistaltic contractions of the ureter. Hagner[15] has observed regurgitation of bladder contents into the renal pelves in two individuals during cystoscopy while the ureteral catheters were *in situ*.

We have repeated Lewin and Goldschmidt's experiments with the main idea of observing the movements of the ureter should regurgitation be found to occur. We have succeeded in duplicating the phenomenon they observed in 10 out of 14 rabbits and also in 1 out of 3 attempts on dogs. The following protocol illustrates the phenomenon as it was observed by us in the rabbit:

Rabbit 1.—Male. Oct. 7, 1919. Ether anæsthesia. A number 7F rubber catheter is inserted into the bladder, the bladder emptied and the urethra tied off with the catheter still *in situ*. A laparotomy is next performed and the ureters are exposed under warm, physiological salt solution. Peristaltic waves can be observed traveling at regular intervals down the ureters, averaging one to two per minute with a speed of approximately 30 to

40 mm. per second. This is watched for some minutes. A syringe containing 20 c. c. is meanwhile filled with warm saline stained with methylene blue. The syringe is attached to the catheter and the methylene-blue solution is gradually injected into the bladder so that it becomes moderately distended. While the ureters are under observation a column of blue fluid suddenly fills the lumen of the right ureter. A peristaltic wave which has already left the renal pelvis meets the ascending column in the upper half of the ureter and impedes its progress. Fresh peristaltic waves commence above, becoming more frequent and vigorous and a struggle ensues for control of the ureter. The column of fluid advances towards the kidney and recedes again with each peristaltic wave. Gradually the peristaltic waves completely expel the methylene-blue solution from the ureter and the uretero-vesical orifice closes. The peristaltic waves quickly subside and resume their former frequency of one to two per minute. This phenomenon repeats itself in a few minutes on the same side and also in the left ureter.

Occasionally the ureters are unable to expel the invading fluid. The following instance illustrates this occurrence:

RABBIT 4.—Male. Nov. 10, 1919. After the initial procedures as described in the preceding experiment have been carried out a column of blue fluid is suddenly seen entering the right ureter. Vigorous peristaltic waves attempt to expel the fluid in the ureter, but after a few minutes it is observed that the ureter is becoming more and more distended with methylene-blue solution while the ureteral contractions are becoming feebler and feebler. Finally, the ureteral movements cease entirely and the invading fluid takes complete possession of the ureter and renal pelvis.

The following experiment is cited as an illustration of the rôle played by peristalsis in regurgitation:

RABBIT 15.—Male. Nov. 13, 1919. Ether anæsthesia. The bladder is emptied and a catheter tied into the urethra as usual. A laparotomy is performed. The ureters are quiescent, no peristaltic waves occur while the ureters are watched for several minutes. Methylene-blue solution injected into the bladder fails to enter either ureter. After removal of the solution from the bladder and reinjection of it several times without any success, 0.5 c. c. of a 1 per cent solution of barium chloride is given intravenously. The musculature of the ureters respond to barium chloride by increased peristalsis and in this instance vigorous peristaltic waves are observed in the ureters immediately after injection. As the first peristaltic waves reach the bladder a column of blue fluid ascends each ureter with great suddenness. The peristaltic waves increase rapidly in strength and frequency and the methylene-blue solution is gradually expelled from the ureters and the uretero-vesical sphincter closed.

The following protocol illustrates the occurrence of the reflux in a dog:

DOG 1.—Female. Nov. 19, 1919. Ether anæsthesia. A number 9F rubber catheter is inserted into the bladder, the latter is emptied and the neck of the bladder tied off with the catheter *in situ*. A laparotomy is performed. Both ureters appear normal and are contracting slowly, twice per minute. A syringe is now attached to the catheter and 30 c. c. of warm methylene-blue solution are injected into the bladder. The last cubic centimeter of fluid has hardly been injected before both right and left ureters and renal pelves suddenly fill with methylene-blue solution. The ureters respond immediately with peristaltic waves of increased frequency and vigor. The methylene-blue solution is completely expelled one or more times from the ureters but immediately reenters them. Finally, the ureters are partially transected midway between kidney and bladder and the methylene-blue solution is observed to flow from them in spurts interrupted by peristaltic contractions.

Regurgitation was observed in the following rabbit on which a complete ligation of the ureter had previously been done:

RABBIT 13.—Female. Nov. 3, 1919. Complete ligation of the left ureter midway between the kidney and bladder.

Nov. 10, 1919. Ether anæsthesia. A catheter is tied into the bladder. A laparotomy is performed. The left ureter is dilated above the ligature and shows no peristalsis. Normal contractions are seen in the portion of the ureter below the tie and on the opposite side. A syringe is attached to the catheter and 12 c. c. of methylene-blue solution are injected into the bladder. Suddenly after a few seconds' interval fluid enters each ureter, on the right side passing up into the renal pelvis, on the left passing up to the level of the ligature. Vigorous peristalsis is initiated in both ureters and continues uninterruptedly without, however, completely expelling the fluid.

A crystal of barium chloride placed on the wall of the right ureter 5 cm. above the bladder produces a characteristic constriction ring from which contraction waves proceed in both directions. As a result, the methylene-blue solution above the constriction becomes imprisoned and is conveyed back and forth in the ureter by a series of peristaltic and antiperistaltic waves. After the barium chloride has been washed off, it takes nearly ten minutes before peristaltic waves originating in the renal pelvis succeed in passing the point where the barium chloride had caused a constriction.

SUMMARY

When a moderate retention is produced in a rabbit's bladder possessing good muscle tone, the uretero-vesical sphincter is occasionally prevented from closing, as it normally does after each gush of urine from the ureter, and the intravesical pressure projects a column of fluid into the ureters. In an animal with quiescent ureters this reflux is difficult to produce. When, however, ureteral peristalsis is stimulated by the injection of barium chloride the bladder content is nearly always regurgitated if there is present a moderate degree of intravesical pressure.

Lewin and Goldschmidt[8] and Marcus[11] believe that antiperistalsis is in many instances responsible for the reflux. In these experiments an antiperistaltic wave preceding the ascending fluid column has not been observed and it is doubted whether reversed peristalsis is ever the cause. The column ascends in our experience at a speed of from 70 to 100 mm. per second, whereas antiperistaltic waves proceeding from a constriction ring in the ureter produced by barium chloride never exceed 40 mm. per second. Furthermore, an observation by Sampson[12] supports our view. He noted that when a cannula was inserted into the uretero-vesical orifice and salt solution passed through the ureter, the ureter responded not by antiperistaltic but by peristaltic waves.

Courtade and Guyon[13] have reported that regurgitation occurs relatively infrequently in dogs, and Sampson[12] was unable to produce it in them at all. From these results Sampson[12] and Young[14] doubt the wisdom of assuming that a comparable phenomenon ever occurs or is even likely to occur in man.

On the other hand, Kretschmer[14] and Hagner[15] have observed regurgitation of fluid from the normal bladder into the ureter during cystoscopy. The former observer believes that the phenomenon noted in man is essentially like that produced experimentally in animals.

It must be emphasized that observations upon cadavers and excised organs are practically valueless in deciding the question of regurgitation. The bladder and ureters in that condition lack tone and peristalsis which, as has been shown, are essential for regurgitation to occur.

All that can be said at present is that regurgitation can be readily produced in the rabbit and somewhat less frequently in the dog. Further observations are necessary before one will be able to say whether a comparable phenomenon occurs in man. Should it occur, it might well be the cause of an ascending infection. It is of course obvious that a reflux of of urine may occur in man when the uretero-vesical orifices are pathologically altered.

Far more scepticism, we believe, should prevail concerning the possibility of the conveyance of organisms up the ureter and the retrograde movements of ureteral calculi by antiperistaltic contractions. We have not observed antiperistaltic waves in the rabbit's ureter in which regurgitation was produced, nor have we observed antiperistaltic waves in those animals in which solid bodies have been introduced into the ureters. The burden of proof still rests with those who attempt to explain ascending infection, so-called retrograde movements of some ureteral stones, or ureteral colic, by antiperistaltic movements of the ureter.

4. The Behavior of the Ureter During Catheterization

We have observed the behavior of the ureter in four normal dogs in which a catheter was inserted through the ureteral orifice. The results were quite uniform.

Ether anæsthesia was used. A catheter was introduced through the uretero-vesical orifice and pushed up the ureter for a distance of from 4 to 8 cm. Normal peristaltic waves were observed passing down the ureter at regular intervals. The majority of them on reaching the tip of the catheter appeared to subside and fail to reach the bladder. Reversed peristaltic waves were never observed originating in the wall of the ureter at the tip of the catheter. On several occasions the tip of the catheter was purposely twisted and moved vigorously upwards and downwards, but even then no abnormal movements of the ureter could be elicited.

Finally, Locke's solution and also sodium bromide were allowed to enter the ureter by gravity through the catheter. The response of the ureter to this procedure was the same in all four dogs. The peristaltic waves travelling down the ureter immediately became stronger and more vigorous. If the injection was stopped, the fluid was gradually expelled and peristaltic activity subsided. If on the other hand the injection pressure was increased, the ureter became distended and peristalsis ceased entirely. Reversed peristaltic movements were never observed during these injections. These observations are similar to Sampson's[12] in which he observed that when fluid was injected into the ureter through a cannula tied into the uretero-vesical meatus, the ureter responded by increased peristaltic waves originating in the renal pelvis and not by reversed peristalsis.

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DEVELOPMENT OF POST-GRADUATE INSTRUCTION IN STRASBOURG NEW FRENCH CLINICS

It is interesting to note the beginning of active post-graduate instruction in the newly organized French University of Strasbourg. Professor Pautrier, at the University Clinic for Diseases of the Skin at the Civil Hospital, is giving a post-graduate course in dermatology and venereal diseases, running from May 1 to July 14. The courses consist of 40 clinical exercises and 10 exercises in the laboratory, amounting to five periods a week. Special arrangements are being made for the students which may permit of their carrying on work during free hours. The honorarium for the course is 300 francs. Arrangements may be made directly through Professor Pautrier.

W. S. T.

THE FATE OF BACTERIA INTRODUCED INTO THE UPPER AIR PASSAGES

V. THE FRIEDLÄNDER BACILLI

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In previous papers [1] we have reported studies on the fate of various bacteria introduced into the upper air-passages. An attempt has been made to analyze the mechanism involved in the disposal of the organisms and as far as possible to interpret its significance. For reasons discussed below it seemed that a study of the Friedländer bacilli would be of particular interest in this connection, and the present report deals with the fate of these organisms after their introduction into the upper air passages.

THE FRIEDLÄNDER BACILLI

Although the name of Friedländer was originally coupled with the bacillus which he observed in cases of pneumonia, a number of organisms are now loosely included in a group under the general designation of the Friedländer bacilli. The characteristics of these organisms may be briefly summarized as follows: Morphologically they appear as short bacilli, often coccoid in form, non-motile and non-spore forming. They are usually surrounded by a well defined capsule which may disappear when they are grown outside the body. The organisms are decolorized when stained by Gram's method. From the point of view of artificial cultivation they may be spoken of as hardy, since they thrive within wide limits of temperature on all the ordinary media. The growth is characteristic, consisting of huge greyish white sticky colonies which tend to become confluent. They may reach a diameter of a centimeter. Various attempts have been made to group these organisms on the basis of sugar fermentation or immunity reactions, but inasmuch as the strains are subject to minor variations no satisfactory classification has been attained. Coulter,[2] however, was able to show that eleven non-lactose fermenting strains derived from various sources represented a single biological group when tested by their reaction to artificial agglutinative sera.

INCIDENCE OF *B. FRIEDLÄNDER* IN DISEASE

Although this organism is not the common cause of lobar pneumonia as Friedländer originally claimed, it does occasionally produce a severe and almost invariably fatal form of pulmonary infection. Sisson and Thompson [3] in 1915 reported four such cases and reviewed the literature. At that time they were able to find records of only 33 cases of pneumonia undoubtedly due to the Friedländer bacillus. During the past eight years two instances of this condition have been observed in the medical wards of The Johns Hopkins Hospital. It is the most picturesque disease process caused by this organism, almost always ending in septicemia and death. Luetscher [4] encountered the Friedländer bacillus twice in 603 sputum cultures made in 459 cases of non-tuberculous respiratory infection. It may also occasionally be found in infected paranasal sinuses, and in middle ear disease where it seems to play the part of a secondary invader. We have obtained it in almost pure culture from the sputum of a patient with a subacute lung abscess. On the whole, then, this group of bacteria play a negligible part in human pathology with the paradox that, when they do produce disease, it is almost uniformly fatal.

INCIDENCE OF *B. FRIEDLÄNDER* IN HEALTHY PEOPLE

The organism is said to be an occasional saprophytic inhabitant of the healthy intestine. It is found but rarely in the mouths and upper air passages of healthy people and can in no sense be regarded as a member of the normal mouth flora. On the other hand, when it is present in the throat it can usually be recovered on repeated examinations over long periods of time—a relatively permanent carrier state exists. On examining a series of 46 people we found Friedländer bacilli in the throats of three. In one case 14 of 16 cultures made during a period of three months showed the organisms, and in another case they were present in 13 of 15 cultures during a period of four months. In neither of these men was there a history of any previous respiratory infection, the throats presented no obvious abnormality and, although they both had chronic cardiac decompensation with œdema of the lungs they developed no autogenous pulmonary infection with these organisms. One of these patients remained in the ward for five months. During this period 285 throat cultures were made on 31 other patients in the same ward. No Friedländer bacilli were found in any of these cultures although the patients were in close contact with the carrier.

We may therefore summarize the rather anomalous conduct of this organism as follows: (1) It occurs very uncommonly in normal throats, but (2) when present persists with great tenacity. (3) There seems to be no tendency for contacts to acquire the organism from a carrier. (4) It very rarely produces disease, and never disease in epidemic form, but occasionally may set up a severe and fatal infection.

In view of the above facts it seemed of particular interest to study the fate of this organism when experimentally introduced into the upper air passages.

METHODS

Three strains were used. *Strain A* was isolated in almost pure culture from an acute purulent sinusitis. The organism possessed the following characteristics:

TABLE I.—FATE OF B. FRIEDLÄNDER SWABBED ON THE TONGUE

Date	Name	Procedure	Number of colonies of B. Friedländer per plate recovered from tongue and pharynx										Control culture before inoculation	
			Tongue				Pharynx							
			After 10 min.	After 2 hours	After 24 hours	After 48 hours	After 10 min.	After 2 hours	After 24 hours	After 48 hours	After 3 days	After 4 days	Tongue	Pharynx
Jan. 12.	S.	One loop of B. Friedländer (Strain A) rubbed on tongue.	∞*	A few cols. F.	No F.	No F.	Many cols. F.	A few cols. F.	No F.	No F.	.....	.....	No F.	No F.
Jan. 13.	E. S.	One loop of B. Friedländer (Strain A) rubbed on tongue.	∞	3 cols F.	No F.	No F.	Many cols. F.	1 col. F.	No F.	No F.	.....	.....	No F.	No F.
Jan. 14.	G.	One loop of B. Friedländer (Strain A) rubbed on tongue.	∞	50 cols. F.	No F.	No F.	100 cols. F.	1 col. F.	No F.	No F.	.....	.....	No F.	No F.
Jan. 15.	L.	One loop of B. Friedländer (Strain G) rubbed on tongue.	∞	30 cols. F.	No F.	No F.	500 cols. F.	200 cols. F.	No F.	No F.	.....	.....	No F.	No F.
Mar. 27.	J.	One loop of B. Friedländer (Strain R) rubbed on tongue.	∞	50 cols. F.	No F.	No F.	∞	20 cols. F.	No F.	No F.	.....	.....	No F.	No F.
Jan. 18.	Hd.	One loop of B. Friedländer (Strain R) rubbed on tongue.	∞	∞	No F.	No F.	∞	∞	No F.	No F.	.....	.....	No F.	No F.
Jan. 13.	St.	One loop of B. Friedländer (Strain G) rubbed on tongue.	∞	Many cols. F.	A few cols. F.	No F.	∞	Several hundred cols. F.	100 cols. F.	200† cols. F.	No F.	No F.	No F.	No F.
April 5.	T.	One loop of B. Friedländer (Strain G) rubbed on tongue.	∞	∞	1 col. F.	No F.	∞	∞	No F.	No F.	.....	.....	No F.	No F.
Mar. 28.	G.	One loop of B. Friedländer (Strain R) rubbed on tongue.	∞	No F.	No F.	No F.	∞	No F.	No F.	No F.	.....	.....	No F.	No F.

*∞ = Innumerable. †Throat a little red. No symptoms.

TABLE II.—FATE OF B. FRIEDLÄNDER SWABBED ON THE NASAL SEPTUM

Date	Name	Procedure	Number of colonies per plate of B. Friedländer recovered from nose and pharynx								Control culture before inoculation	
			Nose				Pharynx					
			After 10 min.	After 2 hours	After 24 hours	After 48 hours	After 10 min.	After 2 hours	After 24 hours	After 48 hours	Nose	Pharynx
Mar. 10.	H.	One loop of B. Friedländer (Strain G) swabbed on left nasal septum.	∞	∞	No F.	No F.	No F.	No F.	No F.	No F.	No F.	No F.
Mar. 8.	C.	One loop of B. Friedländer (Strain G) swabbed on left nasal septum.	∞	∞	No F.	No F.	No F.	10 cols. F.	No F.	No F.	No F.	No F.
Mar. 6.	Co.	One loop of B. Friedländer (Strain R) swabbed on left nasal septum.	∞	30 cols. F.	No F.	No F.	No F.	No F.	No F.	No F.	No F.	No F.
Mar. 8.	J.	One loop of B. Friedländer (Strain R) swabbed on left nasal septum.	∞	1000 cols. F.	2 cols. F.	No F.	No F.	Many cols. F.	No F.	No F.	No F.	No F.
Jan. 14.	W.	One loop of B. Friedländer (Strain A) swabbed on left nasal septum.	∞	∞	No F.	No F.	No F.	A few cols. F.	No F.	No F.	No F.	No F.
April 4.	G.	One loop of B. Friedländer (Strain G) swabbed on left nasal septum.	∞	∞	No F.	No F.	No F.	Many cols. F.	No F.	No F.	No F.	No F.

TABLE III.—FATE OF B. FRIEDLÄNDER INTRODUCED INTO TONSIL CRYPTS

Date	Name	Procedure	Number of colonies per plate of B. Friedländer recovered from crypt and pharynx										Control culture before inoculation	
			Crypt					Pharynx						
			After 10 min.	After 2 hours	After 24 hours	After 48 hours	After 3 days	After 10 min.	After 2 hours	After 24 hours	After 48 hours	After 3 days	Crypt	Pharynx
Mar. 6.	J.	One loop of B. Friedländer (Strain A) placed in a tonsil crypt.	∞	∞	500 cols. F.	No F.	.....	Several hundred cols. F.	100 cols. F.	1 col. F.	No F.	.....	No F.	No F.
Mar. 8.	S.	One loop of B. Friedländer (Strain G) placed in a tonsil crypt.	∞	∞	No F.	No F.	.....	∞	Several hundred cols. F.	No F.	No F.	.....	No F.	No F.
Mar. 10.	U.	One loop of B. Friedländer (Strain R) placed in a tonsil crypt.	∞	Several hundred cols. F.	100 cols. F.	A few cols. F.	No F.	10 cols. F.	200 cols. F.	No F.	No F.	No F.	No F.	No F.

Growth: Large, confluent, opalescent, very viscid stringy colonies.

Morphology: Typical small Gram-negative bacilli. Marked capsule formation.

Sugar Fermentation (24 hours):

	Acid	Gas
Dextrose	+	+
Saccharose	0	0
Lactose	0	0
Mannite	+	+

The first inoculation was made from a subculture on blood agar of the original culture, and thereafter freshly recovered organisms from the experimental inoculations were used. Alteration by artificial growth was therefore reduced to a minimum.

Strain R was recovered practically in pure culture from the sputum of a patient with a lung abscess. Its characteristics were as follows:

Growth: Moderately large (0.5 cm.), confluent, opalescent, very viscid stringy colonies.

Morphology: Typical small Gram-negative bacilli. Marked capsule formation.

Sugar fermentation (24 hours):

	Acid	Gas
Dextrose	+	+
Saccharose	0	0
Lactose	0	0
Mannite	+	+

Strain G was obtained from a healthy carrier who showed no striking abnormality of the upper air passages. The organism was freshly isolated before each inoculation. Its characteristics were as follows:

Growth: Very large (up to 1 cm.), confluent, greyish white, viscid, slightly stringy colonies.

Morphology: Typical small Gram-negative bacilli. Well marked capsule formation.

Sugar fermentation (24 hours):

	Acid	Gas
Dextrose	+	+
Saccharose	+	+
Lactose	Very slight.	Very slight.
Mannite	+	+

These three strains, therefore, included organisms from acute and chronic disease processes, as well as those which were apparently leading a harmless parasitic existence in a carrier.

The methods were the same as those employed in the previous work.[1] Solid masses of a 24-hour growth were swabbed upon the tongue, nasal septum, and in the tonsil crypts of healthy individuals with clinically normal upper air passages, and cultures were made at various intervals on bile agar plates.

EXPERIMENTS

EXPERIMENTS I.—*B. Friedländer* was swabbed on the tongue, and cultures were made from the tongue and pharynx after 10 minutes, 2 hours, 24 hours, and 48 hours. The results are summarized in Table I.

Summary.—B. Friedländer swabbed on the tongue was rapidly spread over the whole mouth cavity. The organisms disappeared with remarkable rapidity. After two hours cultures from the tongue and pharynx in five of nine cases showed only a few colonies. After 24 hours no Friedländer bacilli were recovered from the pharynx in eight of the nine cases. In one instance they persisted for two days and then were recovered no more.

EXPERIMENT II.—*B. Friedländer* was swabbed on the mucosa of the nasal septum and cultures were made from the nose and from the pharynx after 10 minutes, 2 hours, 24 hours, and 48 hours. The results are summarized in Table II.

Summary.—B. Friedländer swabbed on the nasal septum could not be recovered from the nose after 24 hours in five out of six cases. In one instance two colonies were obtained after 24 hours, but none after 48 hours. The organisms were carried rapidly to the pharynx from which they were recovered in variable numbers up to 24 hours.

EXPERIMENT III.—*B. Friedländer* was introduced into tonsil crypts and cultures were made at various intervals for several days from the crypts and from the pharynx. The results are summarized in Table III.

Summary.—Friedländer bacilli deposited in tonsil crypts disappeared rapidly, although they persisted a little longer than when swabbed on the free surface of the mucous membranes. This was probably due to mechanical retention, as there was no evidence of any lesion and the organisms were eliminated in from one to two days.

In summary, then, *B. Friedländer* experimentally introduced into the upper air passages in various ways disappeared rapidly—usually in less than 24 hours. There was no tendency to the production of a carrier state and no disease was set up.

THE MECHANISM OF THE DISPOSAL OF *B. FRIEDLÄNDER*

In the previous studies on the fate of organisms placed in the upper air passages, we attempted an analysis of the factors involved in effecting their rapid disposal. It became apparent that, as a rule, the mechanical flushing action of the secretions was the most important means of eliminating foreign organisms, and this principle seems to apply to the Friedländer bacilli as well. The effect of saliva on the growth of these organisms was studied *in vitro*. They survived and multiplied for days in salivas of various reactions, readily overgrowing the ordinary mouth bacteria. An illustrative protocol is shown in Table IV.

TABLE IV.—EFFECT OF SALIVA ON THE GROWTH OF B. FRIEDLÄNDER

Time of culture (one loop of mixture from each tube plated)	Tube 1. 0.5 cc. saliva	Tube 2. 0.5 cc. salt sol. + 1 loop B. Friedländer	Tube 3. 0.5 cc. saliva + 1 loop B. Friedländer
Immediately	Mouth flora.....	∞ Friedländer	∞ Friedländer + mouth bacteria.
After 4 hours (37°).	Mouth flora.....	∞ Friedländer (but fewer).	∞ Friedländer + mouth bacteria.
After 1 day (37°)...	Mouth flora.....	∞ Friedländer (but fewer).	∞ Friedländer + mouth bacteria.
After 2 days (37°)..	Mouth flora.....	50 cols. Friedländer.	∞ Friedländer + fewer mouth bacteria than in previous culture.

DISCUSSION

In previous experiments it was shown that various organisms—*Sarcina lutea, B. coli, Staph. albus,* and *B. influenzæ*—introduced into the upper air passages of normal individuals disappeared with great rapidity—usually within 24 hours. This rate of elimination was found to correspond with the speed of disappearance of inert particles, and a longer persistence in occasional cases was explained on a mechanical basis. It seemed that the normal intact mucous membranes offered no opportunity for colonization or invasion by these organisms, but that they were impervious much as the normal intact skin surfaces are. To the above list of bacteria *B. Friedländer* may now be added. It appears that a variety of strains freshly isolated both from disease processes and from the throat of a healthy carrier disappear at the usual rate of speed—usually within 24 hours.

These facts, which are quite in harmony with the observations on contacts mentioned above, do not explain the mechanism of the chronic carriers found among normal people, nor the occasional cases of severe infection due to this group of organisms. They bring strong support, however, to the impression gained from epidemiological study that the rôle of the Friedländer bacillus in disease is essentially one of a secondary invader, and that when it produces disease which is apparently primary, a very special set of favoring circumstances must be present.

CONCLUSIONS

1. Friedländer bacilli freshly isolated from various sources were introduced into the normal upper air passages without producing local or general disease.
2. The organisms disappeared rapidly—usually within 24 hours.
3. It was not possible artificially to produce a carrier state.
4. The bacteria are removed by mechanical means.
5. This group of organisms when associated with disease usually act as secondary invaders.

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A PHYSIOLOGICAL STUDY OF THE EUSTACHIAN TUBE AND ITS RELATED MUSCLES

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The tympanic membrane functions perfectly only when the atmospheric pressure is the same on both sides of it. The tension resulting from an inequality in pressure may cause severe pain from the bulging and stretching of the membrane, may even be sufficient to rupture it, and in all cases impairs its vibratory function until the pressure equilibrium is again restored. This equalization of pressure is made possible by the inflow of atmospheric air from the nasopharynx through the Eustachian tube into the tympanic cavity until the tension of the air within this cavity becomes identical with that of the air in the external auditory canal. It is a matter of common knowledge that sudden changes in atmospheric pressure may so affect the ear-drum that its proper functioning is disturbed, and the exposure of aeronauts to such conditions is, of course, a matter of history. During the late war, however, interest was more forcibly attracted to this subject, since aviators in the service, while making sudden changes in altitude, often suffered distressing difficulties referable to the ear-drum. This study was begun, at the suggestion of Dr. W. H. Howell, in the effort to learn something of that part of the physiology of the Eustachian tube which is concerned with its action as a protective mechanism of the ear-drum. It was believed that, perhaps, a clear understanding of this mechanism might disclose some simple associated movement through which an opening of the Eustachian tubes could, when necessary, be effected quickly at will. At the outset, however, it must be confessed that these experiments have led to no new or peculiarly efficient voluntary method of dilating the tubes. The physiological mechanism of the Eustachian tube was found to be linked with certain reflexes described below, and the study of this mechanism has led to the belief that those who state that they are able quickly and efficiently to open their Eustachian tubes by protrusion of the lower jaw and other similar movements are more probably erroneously interpreting various synchronous but dissociable aural sensations (such, for instance, as the rumble produced by the contraction of the tensores tympani) as a dilatation of the tubes. Nevertheless, on the physiological side, a certain amount of information has been acquired during this study, which, it is hoped, may serve to lessen somewhat the confusion and uncertainty which pervades the literature concerning three points of fundamental importance in any consideration of the physiology of the Eustachian tube: (1) The physiological conditions under which the tube is open; (2) the muscles which influence the patency of the tube; (3) the innervation of those muscles. The present paper is concerned only with the first two of these questions. Experiments bearing upon the nerve supply of the palatal muscles in the region of the Eustachian tube will appear in a separate report.

I. The Physiological Conditions Under Which the Tube is Open

Eustachius, in the sixteenth century, described the tube connecting the tympanic cavity with the nasopharynx. He believed that this tube normally was open; and up to 1853

the two cavities were generally considered to be always continuous, this condition being supposed to be necessary for perfect hearing. It was Toynbee,[1] in 1853, who first definitely insisted that the pharyngeal orifice of the tube normally is closed, and that it is opened during deglutition to permit an inflow of air. He arrived at this conclusion especially from a consideration of his now well-known experiment of swallowing with both mouth and nose closed, which causes a feeling of tension of the tympanic membranes because of the disturbed air-pressure within the Eustachian tubes. If now the mouth and nose be opened, a return to the normal pressure-balance should occur immediately if the pharyngeal orifices of the tubes be always open. No such change occurs, however, until a second swallowing movement is performed with the nose open; but this is invariably accompanied by a relief of the pressure sensations, indicating that the tubes have opened during the act to admit atmospheric air from the nasopharynx.* Toynbee noted, further, the practice of swallowing to relieve the inequality of pressure on the two sides of the ear-drum which occurs during descent in a diving bell, as the pressure in the external auditory canal continually increases.

In 1861 Politzer[3] devised a little manometer to be fitted into the external auditory canal, which, he claimed, would indicate pressure changes within the Eustachian tube because of the consequent displacement of the tympanic membrane. From a rise of the fluid level during swallowing he concluded that the tube opens during the reflex to admit an inflow of air. Jago,[4] however, after repeating these experiments, wrote that Politzer's manometer is subject to too many sources of error to be productive of any reliable information. On the anatomical side, Von Tröltsch[5] shortly afterward deduced from a careful study of the relations of the muscles of the region that normally the tube is closed but must open during deglutition.

With the invention of the rhinoscope and nasopharyngoscope a more direct method of observing the pharyngeal orifice of the tube became available; and Cutter,[6] from his rhinoscopic studies in 1867, states most positively that normally the tubal orifice is open but that it closes during swallowing. Cleland[7] came to the same conclusion as a result of his own observations in 1868; and indeed Cutter's continued studies[8] led him in 1872 to the conclusion that "the Eustachian tubes are open at all times" during the swallowing reflex as well as while at rest. In 1873 Rumbold[9] records the opposite conclusion from his experiments and clinical observations that "during the act of deglutition the Eustachian tube is not an open passage into the tympanum," but that the tubal walls are always in slight contact. General opinion at that date, however, seemed to lean toward the view of Politzer and Von Tröltsch—that the tube is closed when at rest and opened during deglutition; but it was an opinion unverified and further conflicting experiments and observations served to intensify the uncertainty. Thus, in 1880, Fournié[10, 11] described his experiments on the Eustachian tube and wrote:

"Contrairement à l'opinion généralement adoptée de nos jours, la trompe d'Eustache est toujours ouverte, et la communication de l'air extérieur avec celui de la cavité du tympan est incessante. L'obturation de la trompe n'est jamais que momentanée et elle se produit jour et nuit pendant les mouvements de deglutition, pendant la prononciation de certaines lettres, pendant le chant."

Semeleder,[12] from rhinoscopic observations, described a narrowing of the pharyngeal orifice accompanying every elevation of the soft palate; and Lucae[13] concluded from his studies on human subjects that "with vigorous elevation of the soft palate, also during swallowing and phonation, there occurs a closure of the mouth of the tube" which "is again opened when the soft palate descends." In another study of the Eustachian tube Lucae[14] records his observations which led him to believe that the tubal orifice opens during expiration and closes during inspiration: "Bei sehr tiefer Inspiration fand sojar ein volliger Verschluss der Tubamundung stat, wahrend dieselbe bei expiration deutlich klaffte"; and in 1903 Patel,[15] observing directly the tubal orifices in a patient who had suffered a neoplasmic erosion of the flesh and bone on one side of the face, described vague movements of opening and closing of the tubal orifices during respiration.

From their respective experiments, Dionisio[16] in 1912, and Bilancioni[17] in 1914, arrived at the conclusion that the tube is normally closed, and opens during swallowing; whereas Caldera[18] in 1915 wrote in refutation of their work that one cannot limit the opening of the tube to the periods of deglutition, his observations apparently demonstrating that the Eustachian tubes, under normal conditions, are always open.

Among present-day texts we find Piersol[19] stating that the tube is normally closed, but is opened during deglutition, mouth-breathing, and whenever the palate is raised. Cunningham[20] is more non-committal: "During the act of swallowing it is generally thought that the auditory tube is opened by contraction of the tensor veli palatini muscle which arises from it. It has been held, on the other hand, that the auditory tube is closed during swallowing by compression of its wall by the contraction of the levator veli palatini."

EXPERIMENTS

Politzer[3] has pointed out that the muscular relations of the Eustachian tube of the dog correspond closely with those of man. This close similarity of regional anatomy was confirmed during the present work by comparisons of dissections of embalmed human subjects and formalin specimens of dogs' heads; and further by comparisons of dissections of the region, made upon the unembalmed bodies of human subjects at the autopsy table, with the dissections made upon anesthetized dogs during these experiments. Dogs, therefore, were used in all of the animal experiments described in this paper.

The exposure of the pharyngeal orifices of the Eustachian tubes can be carried out in the following manner: A dog is

* It is interesting to note that although this experiment now bears Toynbee's name, Maissiat[2] had written fifteen years previously: "Qu'on se tienne le nez pincé, la bouche étant close, et qu'on fasse effort pour inspirer, l'ouie est assourdie d'une certaine manière; les narines étant redevenues libres, avalez quelquechose, votre salive, l'ouie se rétablit parfaite."

anesthetized, tracheotomy performed and connection established with an ether-respiration apparatus by means of a tracheal cannula. Both common carotid arteries are ligated to minimize hemorrhage, as it is desirable to introduce about the delicate palatal muscles as few ligatures as possible. The immediate collateral circulation is ample to maintain satisfactorily the nutrition of the structures during the experiment. A mouth-gag is introduced to hold the jaws widely separated and the tongue is drawn forward and stitched to the lower lip. The hamular processes of the pterygoid bones can be felt on either side as distinct, bony prominences in the roof of the mouth. Using these as landmarks, an incision is made through the soft palate from a point about one centimeter anterior to them, extending backward in the mid-line almost to the insertions of the levatores palati in the uvular region. This incision exposes the nasopharynx, so that the orifices of the Eustachian tubes can be clearly seen, situated on either side just posterior to the hamular processes of the pterygoid bones. In some experiments the fibrous expansion of the tendons of the tensores palati (which forms a fascial layer of the soft palate) was exposed intact, in order to study the action of that muscle. In almost all cases, the midline insertions of the levatores palati were left uncut, since a perfect exposure of the tubal orifices may be obtained without their destruction.

The orifices of the Eustachian tubes appear as slits in the mucous membrane of the nasopharynx. The anterior lip of the slit consists of fibrous tissue covered with mucous membrane which extends into the tube. The posterior cartilaginous lip appears as a curved prominence beneath the mucous membrane. The two lips are plainly seen to lie, normally, in contact; *i. e.*, the tubal orifice is normally closed, when at rest.

Deglutition is readily effected by mechanical stimulation of the pharynx. Invariably the swallowing reflex is accompanied by a wide gaping of the tubal orifices. This gaping can be seen to be brought about by the membranous wall being drawn anteriorly away from the cartilaginous wall, the latter undergoing no appreciable change of position, although the mucous membrane about it is somewhat disturbed by the contraction of the underlying levator palati muscle. The opening of the tube is quite sudden and brief, and occurs at the moment of greatest contraction of the upper pharyngeal muscles—when the hyoid bone is at the height of its ascent. Nasopharyngoscopic observations upon normal human subjects also show clearly that there occurs a gasping dilatation of the mouth of the tube during deglutition; and this opening of the tube appears similar in all important respects to the process as observed in the dog.

During the most forced respirations which can be elicited reflexly by the stimulation of sensory nerves, the pharyngeal orifices of the tubes remain closed, even though the palate is being elevated vigorously by the levatores palati, which, by reason of their contractions during forced respiration—a phenomenon which has been invariably observed during these experiments—seem to warrant consideration as accessory muscles of respiration.* Their contractions will be synchronous with inspiration or expiration depending upon which of these movements is the "active" and more prominent one during forced respiration. It has been held that "whenever the palate is raised . . . . the tensor palati and levator palati contract, and in so doing open the Eustachian tube."[19] Elevation of the palate, alone, is certainly not accompanied by an opening of the Eustachian tube. It will be shown that the contraction of the tensor palati muscle is the *conditio sine qua non* of every physiological opening of the tube; and simple levation of the palate is by no means invariably accompanied by a simultaneous contraction of the tensor palati—a fact which can be clearly determined by watching directly the naked muscles during forced respiration in a preparation such as will be described below; the levator will be seen to execute definite respiratory contractions, while the tensor remains perfectly at rest and the tube remains closed.

A study of the pharyngeal orifices of the Eustachian tubes in human subjects, by means of the nasopharyngoscope, allows one to understand, perhaps, why the literature contains conflicting statements about them; for there are, clearly, individual differences in the appearance of the orifices. Furthermore, there are observed variations in the reactions of the orifices in the same individual at different times, so that during forced respiration or elevation of the palate produced by the enunciation of "Ah" or "U," there will be seen at one time only a disturbance of the fold of the mucous membrane which overlies the contracting levator palati muscle, the tubal orifice remaining closed, whereas at another time the same individual will exhibit what appears to be an actual opening of the orifice during these movements. But it should be recognized that it is very difficult to draw any very clear-cut conclusions from nasopharyngoscopic observations of slight movements of the mouth of the tube, for the orifice itself lies almost hidden within a funnel-shaped hood, the mucous membrane of which is disturbed by almost every movement of the soft palate, and shadows produced by the movements of this region are perhaps not so easy to interpret as has been assumed. Careful observation of the orifices in human subjects will allow here, then, only the following statements: During quiet respirations the orifices remain closed; during elevation of the palate, whether by forced respiration or by other means, there is usually seen only a disturbance of the mucous membrane, brought about by the contraction of the underlying levator palati muscle; in some instances there has appeared a disturbance of the membrane to such a degree that the orifice appeared somewhat dilated, but in no case did there occur during elevation of the palate the unmistakable wide gaping of the orifice which is so strikingly seen during swallowing. It is not impossible that contraction of the tensor palati may occur synchronously with elevation of the palate at times other than during the swallowing,

* Debrou [21] noted clinically the elevation of the palate during forced inspiration, and quotes Albinus [22] as having also been aware of this.

yawning and sneezing reflexes; and such elevation of the palate would consequently be accompanied by an opening of the tube. But elevation of the palate without opening of the tube is to be regarded as the rule, for this is clearly true in the dog; and further, if Toynbee's experiment be followed by forced respiration, or by elevation of the palate produced by the enunciation of "Ah" or "U," no equalization of pressure within the tube will occur. In no instance was there seen during elevation of the soft palate the narrowing of the orifice which has been described and assumed to occur as a theoretical effect of the contraction of the levator palati muscle. On the contrary, the palate is vigorously elevated during deglutition and it is during this act that the orifices are most widely gaping.

It has been held [32] that the tube is opened by mouth breathing; and it has been suggested that the virtue of the unconscious opening of the mouth in attentive listening may be associated with the patency of the tube accompanying such a position. The present experiments, however, were all made upon animals breathing with wide-open mouths, and the tubal orifices were clearly seen to be closed. Nasopharyngoscopic observations made upon human subjects also showed that there occurs no dilatation of the ostium during mouth-breathing; nor was there seen any change in the condition of the orifice in subjects who were requested to listen concentratedly, with the mouth open, for the ticking of a watch which was gradually brought within the range of hearing. And indeed, if the experiment of swallowing with the mouth and nose closed be followed by mouth-breathing with attentive listening, no restoration of pressure balance will result. Hence we must conclude that the Eustachian tube is not opened during this maneuver. It has long been believed that "concussion of the tympanic membrane from loud reports is minimized by mouth-breathing," [33] and the reason assigned has been the supposed accompanying opening of the tube. It is not improbable that mouth-breathing merely offers a larger portal of entry into the nasopharynx for the concussion waves which may force themselves into the Eustachian tubes after the manner of air in the Valsalvian experiment; and in such a way there will be exerted an equal pressure effect upon both sides of the tympanic membrane; but any such effect of mouth-breathing which may exist cannot be ascribed to a consequent patency of the Eustachian tube.

During many hours of observation, the tubal orifices of dogs have never been seen to open independently of the swallowing reflex; they exhibit neither periodic nor irregular independent reflex dilatations. It was thought, however, that perhaps the mere existence of a difference in pressure on the two sides of the tympanic membrane might be a sufficient stimulus to set in motion a reflex opening of the tube and a consequent restoration of pressure-balance. Certainly the pressure inequality brought about by swallowing with the mouth and nose closed is followed by no such reflex equalization of pressure; and it is well known that many persons are at a loss to know what they can do to relieve the pressure disturbance experienced during transit through the Hudson tubes—a fact which argues against the existence of any reflex adjustment. Further, Green,[33] in a report of his studies on the effects upon the Eustachian tube of descent in a diving-bell, described the actual rupture of the tympanic membrane owing to the inequality of pressure exerted upon it; and he states that this occurred especially in persons uninstructed in the method (swallowing) of restoring the pressure-balance on the two sides of the membrane. Indeed, it will be remembered that it was the apparent lack of such a reflex adjustment in the case of aviators which led to the present study. However, in pursuit of the possibility of a reflex adjustment, the atmospheric pressure in both external auditory canals was raised greatly by means of rubber atomizer bulbs, which were sealed into the ears of anesthetized dogs. No opening of the tubes occurred; nor did this pressure disturbance set in motion a swallowing reflex as a means of opening the tubes. Blasts of air were directed against the pharyngeal orifices without effect; nor did mechanical stimuli or increased air pressure within the tubes cause either an independent dilatation or a swallowing reflex. It appears that the swallowing reflex, as a means of equalizing the atmospheric pressure on the two sides of the tympanic membrane is consciously (often habitually), but not reflexly, subservient to the demands of the membrane; and the opening of the tube during deglutition, although a most important function, is, however, merely a by-product of this frequent reflex. Certainly, the existence of an inequality of pressure on the two sides of the tympanic membrane is not, in itself, a stimulus that will set in motion a reflex opening of the tubes and a consequent restoration of pressure equilibrium.

In human subjects the tubal orifices were seen to open reflexly only during deglutition and sneezing.* Attempts were made during several hours to watch the orifices during the yawning reflex, but the presence of the nasopharyngoscope within the upper respiratory passage inhibited completely the execution of this reflex. However, it is certain that the Eustachian tubes are opened during yawning, for if the middle ears are inflated either by Toynbee's or by Valsalva's experiment (forced expiration with mouth and nose closed) a yawn will bring about a restoration of pressure-equilibrium which is usually even more satisfactory than that attendant upon the swallowing reflex. One derives the distinct sensation that the tubes are held open during the yawning reflex for a longer period of time than during deglutition. It is, therefore, not true that "of all the movements of the muscles of the soft palate, there is none which exercises such an influence in opening the tube as the act of swallowing." [34] The dilatation of the Eustachian tubes must be regarded as a most important function of the yawning reflex, for the tubes are ventilated during this act with a peculiar thoroughness.

*** The opening of the tubal orifice during sneezing was seen during a nasopharyngoscopic examination of a human subject by Dr. E. N. Broyles, to whom the writer is greatly indebted for his interest and assistance which made possible the clinical nasopharyngoscopic observations recorded here.**

However, what has been said concerning the relation of the swallowing reflex to the pressure-balance on the tympanic membrane is applicable also to the yawning reflex; for a disturbance of the pressure-balance will not provoke a yawning reflex as a means of restoring equilibrium.

II. The Muscles Which Influence the Patency of the Tube

Discussing the opening of the Eustachian tube during the act of swallowing, Yule[28] wrote: "Owing to the extreme complication of the act, no observer has yet been able to ascertain which the efficient salpingeal muscles are"; and up to the present time no satisfactory experimental evidence has been brought to bear upon this question.

The tensor palati muscle (tensor veli palatini; sphenostaphylinus; circumflexus palati; external peristaphylin) * and the levator palati muscle (levator veli palatini; salpingostaphylinus; internal peristaphylin) by reason of their intimate anatomical relations to the Eustachian tube have long been associated with the physiology of this structure. In 1707 Valsalva,[29] after describing the tensor as a "Novus Tubæ Eustachinæ Musculus," drew attention to its attachment along the membranous wall of the tube and regarded the muscle as a dilator of this structure. The levator palati he termed the "salpingostaphylinus," because of its close anatomical relation to the tube. About the tensores and levatores palati muscles has centered the greater part of the discussion concerning the movements of the Eustachian tube.

In 1853, Toynbee[1] revived Valsalva's original conception that the tensor palati is a dilator of the Eustachian tube. Politzer[3] was convinced of this; and in 1864 Von Tröltsch[5] published his careful anatomic studies on the relation of the tensor to the tube. He believed that it must act as a dilator and wrote: "The problem is to prove on anatomical grounds that, during the act of swallowing, the tensor palati has (or gains) a fixed point below, so that the fibers arising from the membranous portion of the tube are able to carry out their activity in this direction." He concludes that during deglutition the soft palate becomes this "fixed point." It will be shown below that no such fixation of the soft palate is necessary for the action of the tensor upon the tubal wall.

Most writers, more from a consideration of the attachment of the tensor palati all along the membrano-cartilaginous wall of the tube than from actual physiological observations, are agreed that this muscle during contraction must dilate the tubal lumen, if not the orifice as well. There are, however, observers who oppose this view. Thus Cleland[7] in 1868, from his dissections and from observations upon the Eustachian tube in a case of destructive ulceration of the soft palate, was led to doubt the efficacy of the tensor palati as a dilator of the tube; and in 1878 Yule's studies[28] brought him to the same conclusion. Rumbold,[9] in the same year, believing from his experiments and clinical observations, that the walls of the tube are always in slight contact, was convinced that the tensor cannot dilate the tubal lumen. Fournié,[30, 31] in 1880, studied the action of the tubal muscles and, believing that the tube is normally open, regarded the tensor as an active constrictor of the Eustachian tube, having the function of closing the tube during deglutition. Bryant,[27] in 1907, discussing the action of the tensor on the basis of his anatomic and nasopharyngoscopic studies, wrote that "contractions of the muscle can affect the lumen of the tube but little, if at all." Mouret and Rouvière[25] believed that the tensor acts as a dilator of the tube, but sharply limited the action of the muscle to the superior portion of the tube, stating that its contraction can have no effect whatever upon the pharyngeal orifice, or the portion of the lumen immediately adjacent thereto.

Concerning the levatores palati muscles there also exists a considerable divergence of opinion. Toynbee[1] believed that the levator acts as a synergist to the tensor in its function of opening the Eustachian tube. Von Tröltsch[5] concluded from his anatomical studies that this muscle is a constrictor of the tube, acting as an antagonist to the tensor, its belly during contraction pressing against the tubal wall and so tending mechanically to narrow the lumen. In 1862 Semeleder[33] (rhinoscopic observations) wrote that the levator, during contraction, narrows the pharyngeal orifice of the tube. Luschka,[35] in 1868, held that the levator closes the tube, and Cleland's observations[7] brought him to the same opinion. Politzer[34] believed that the muscle narrows the pharyngeal orifice but widens the lumen of the tube. Fournié,[30, 31] in 1880, described his experiments which led him to believe that the levator constricts the lumen of the tube. In 1903 Mouret and Rouvière[25] affirmed from anatomical considerations that the levator opens the pharyngeal orifice and the adjoining portion of the tubal lumen, while the remainder of the tube is dilated by the tensor palati, as has been already stated. They believed that only by the combined action of the two muscles could the tube be opened throughout its entire extent. In 1906, Panier[26] considered the levator as a tubal constrictor; while in 1907, Bryant[27] (anatomic studies and nasopharyngoscopic observations) regarded the levator palati as the muscle chiefly responsible for the opening of the tube and accordingly designated it as the "dilator tubæ," a name which had hitherto been applied to the tensor palati. Reference to con-

* "The tensor palati arises from the inferior surface of the sphenoid bone and the inner plate of the pterygoid processes; a great number of its fibers also arise from the short, hook-like, lateral cartilaginous wall, and from the membranous part of the tube. In its downward course its flat belly lies close to the lateral wall of the membranous tube and is rather firmly attached to it. The direction of its fibers forms an acute angle with the cartilaginous part of the tube and its tendon, winding around the hamulus pterygoideus, radiates into the fibrous prolongation of the hard palate. The tendon of the muscle is so tightly attached to the hamular process that the effect of its contraction is greater on the Eustachian tube than on the soft palate."

"The levator palati arises from the inferior surface of the petrous bone bordering on the carotid canal. Its rounded belly runs parallel to the Eustachian tube, is closely applied to the membranous portion which forms the floor of the tube and is inserted in a radiating manner into the soft palate below its pharyngeal orifice. None of its fibers arise from the Eustachian tube as was formerly believed, but the muscle is attached to it only by a small amount of connective tissue."[34]

temporary texts leaves one uncertain. Piersol[29] writes: "In addition to opening the tube, the levator elevates its floor"; Spalteholz[31] gives as the action of the levator: It "narrows the ostium pharyngeum and widens the isthmus tubæ"; Cunningham[30] summarizes this diversity of opinion by the statement (quoted above) that some believe that, during swallowing, the contraction of the tensor opens the tube, while others hold that the contraction of the levator closes it during this act.

Whereas the greater part of the discussion concerning the movements of the Eustachian tube has centered about the tensor and levator palati, there have been experimenters and clinical observers who have insisted that other muscles may be concerned. Thus, according to Packard,[32] the palatopharyngeus muscle has an auxiliary action in the opening of the tube; and, indeed, Yule's studies[33] brought him to the view that this muscle is the chief tubal dilator, and that "the tensor and levator palati can have no participation in the opening of the tube." Gellé,[34] as a result of his own experiments, adds the superior constrictor of the pharynx to the list of muscles which have been regarded as dilators of the tube, while many authors speak hazily of the salpingo-pharyngeus muscle.

It is clear that further speculation, based upon anatomic grounds, or upon indirect physiological observations such as the attempts to interpret the functions of these muscles while they are hidden by the nasopharyngeal mucous membrane would be worth very little. In the present study the attempt was made, therefore, to lay bare all of these muscles in the living animal by careful dissection, leaving their nerve supplies intact; then, by electrical stimulation of the individual muscles, to determine the action of each upon the Eustachian tube; and finally, to observe directly their various actions during the reflexes which have been supposed to affect the Eustachian tube.

EXPERIMENTS

After preliminary tracheotomy and ligature of the carotids, the muscles about the Eustachian tube can be exposed for study in anesthetized dogs in the following manner: A midline incision is made through the mucous membrane of the soft palate and dissection is carried lateralward along the plane of the fibrous layer formed by the tendinous expansions of the tensores palati. The hamular process of the pterygoid bone is exposed and the palatopharyngeus muscle is seen, stretching from this point backward toward the pharynx. Careful separation of the fibers of this muscle from those of the closely associated pterygopharyngeus reveals the levator palati, which passes between them on its way to the soft palate, forming with them an angle of about 70°. The dissection is continued across the hamular process and the internal pterygoid muscle is seen just lateral to this landmark, extending anteriorly along the palatine bone. This muscle completely hides the tensor palati in such an approach. It is therefore necessary to remove the overlying fibers of the internal pterygoid in order to expose the tensor palati, which can then be seen as a rather pale, very small muscle, the fibers of which extend from the pterygoid hamulus lateralward, backward and upward toward the inferior portion of the temporal bone. If a probe is now passed into the pharyngeal orifice of the Eustachian tube through an opening in the soft palate, the membrano-cartilaginous portion may be followed up to the beginning of the osseous portion, and the fibers of the tensor palati will be seen to be attached along the wall of the tube, the membranous side of which can be freely moved by traction upon this muscle.

Some observers have believed that the muscle fibers usually designated as the tensor palati are divisible, in reality, into two separate muscles, one having the function of making tense the soft palate, and the other that of opening the Eustachian tube. It is not possible by dissection, either in the dog or in human subjects, definitely to separate the tensor palati into two distinct muscles; and a microscopical study demonstrates that it is quite uniformly composed of striated fibers which are separated at no point by an intercalated epimysium. However, especially in dissections of formalin preserved specimens of dogs' heads, one is able to understand the basis of such a suggestion; for dissections may be made in which a portion of the fibers of the tensor appear to rise from a firm attachment to the hamular process of the pterygoid bone and to be inserted along the membranous wall of the tube, while the remaining fibers arise from the skull adjoining the osseous portion of the tube and converge into a tendon which glides, freely movable, over the hamular process to expand into its fibrous insertion in the soft palate. Both portions of the muscle, however, are enclosed in the same facial sheath.

In the dissections made upon the anesthetized animal for experimental studies, care was taken to leave uninjured the nerve supply of each muscle. The integrity of the nerve supply was, in all cases, tested after completing the dissection by watching for the contraction of the individual muscles during the execution of the swallowing reflex in which they normally participate.

In such a vivisection as has been described, the muscles in the region about the Eustachian tube may be stimulated electrically either individually or in groups, and their respective actions upon the tube may be directly observed; for the entire region, containing the various muscles (naked throughout their extent), and the pharyngeal orifice of the tube as well, lies clearly exposed before the eyes.

The internal pterygoid is the largest of the muscles which lie near enough to the tube to suggest a possibility of action upon that structure. Its close apposition to the tensor palati, and so to the membranous wall of the canal, has already been mentioned; and it is an interesting fact that both Eustachian tubes of birds open into the midline of the pharynx through a single, common membranous canal, the patency of which is governed physiologically by the action of the adjacent internal pterygoid muscles.[3] Further, it has been held that, in man, the Eustachian tubes may be opened by protrusion of the lower jaw (*i. e.*, by contraction of the internal pterygoids). This muscle was therefore stimulated in the dog, but its con-

traction was seen to be entirely without effect upon the pharyngeal orifice of the tube.

Stimulation of the palatopharyngeus, the pterygopharyngeus or the superior constrictor muscle of the pharynx causes no change in the condition of the tubal orifice.

Stimulation of the levator palati muscle does not affect the orifice in any way. There occurs, during its contraction, no dilatation whatever, nor is there seen the narrowing of the orifice which has been assumed to result as a theoretical effect of the bulging of this muscle during contraction. The only effect of the contraction of this muscle (aside, of course, from its action upon the soft palate), which can be observed by inspection of the nasopharynx, is a disturbance of the mucous membrane immediately overlying its belly. This is seen when only the lateral surface of the muscle is exposed for stimulation.

When the tensor palati is stimulated, its contraction is accompanied by a wide gaping of the pharyngeal orifice of the tube and a tension of the fibrous expansion of its tendon in the soft palate. It can be seen that this latter effect does not actually modify the condition of the soft palate very much, for it appears to be concerned chiefly with that portion which is immediately adjacent to the hard palate—the so-called "fibrous prolongation of the hard palate" mentioned by Henle; and this "fibrous prolongation" possesses a definite stiffness even when the tensor palati is at rest. The dilatation of the tubal orifice is clearly seen to be caused by the muscle, during its contraction, pulling against its attachment to the membranous wall of the tube, and so drawing this portion away from the cartilaginous wall with which it lies in contact in the resting condition. Henle[3] believed that the the tensor opens the tube by its action upon the upper, hook-like portion of the cartilaginous wall. Undoubtedly the tensor has fibers of attachment along this cartilaginous border as well as along the membranous wall of the tube and it is possible that these fibers may actually unfold this scroll-like border to some extent. However, one can clearly see that it is the lower margin of the orifice which is most widely dilated during the contraction of the tensor palati; and it is also distinctly seen that the muscle lifts the membranous wall away from the cartilaginous chiefly by simple traction upon it.

Von Tröltsch, in his discussion of the physiology of the Eustachian tube,[5] suggests the following theory to explain the action of the tensor (and levator) palati upon the tube: "During deglutition the soft palate, through the action of the lower muscles (glosso-palatine and pharyngo-palatine), is stretched downward and back and is pressed against the posterior wall of the pharynx. But a contraction occurs simultaneously in the antagonists of these muscles, the upper muscles of the palate (tensor and levator palati), which will change points of fixation and attachment in such a way that the soft palate will become the (relatively) fixed point, and the movable wall of the tube the point of origin of the muscular fibers from which motion proceeds." Jago[4] also laid stress upon such a "fixation" of the soft palate as a necessary precursor to the action of the tensor palati. In the present experiments, however, the palatal insertion of the tensor was found to be quite unessential to the dilatation of the tube; for the fibrous expansion of the tendon of this muscle may be cut through in its entire extent, eliminating any possibility of its action as a "fixed point," and nevertheless stimulation of the tensor or its contraction during the swallowing reflex will cause quite as wide a dilatation of the tubal orifice as that which occurs when the palatal insertion is left intact. The attachment of the tensor palati to the hamular process of the pterygoid bone seems to be the only fixed point necessary for the action of this muscle upon the tube; and, indeed, Von Tröltsch himself has remarked upon the extraordinary strength of this attachment. Moreover, the fact that stimulation of the levator palati failed to cause any change in the condition of the tubal orifice cannot be said to be a result of a lack of "fixed point" in the palate against which this muscle might pull; for the palatal insertion of the levator has been grasped with forceps and held immovable during stimulation of the muscle, and, although in some cases actual traction was exerted upon the palatal insertion, the tubal orifice remained entirely unaffected during the most vigorous contractions of the muscle.

That the tensor palati alone effects the dilatation of the tubal orifice was determined by cutting in turn the palatopharyngeus, the levator palati and finally the tensor palati, while the effect of the swallowing reflex upon the orifice was observed after the severance of each muscle, all of which normally contract during deglutition. The orifice was widely opened during each swallowing reflex with no appreciable variation in extent until the tensor had been cut, whereupon the reflex was no longer accompanied by the slightest opening of the tube. The experiment was then reversed; the tensor having been cut first, the swallowing reflex was accompanied by no dilatation of the orifice whatever, although both of the other muscles were intact and contracting vigorously. A similar type of experiment was performed by stimulating the muscles electrically; and it was found that stimulation of the tensor alone, after cutting the two other muscles caused a wide gaping of the pharyngeal orifice of the tube; whereas, if the tensor were cut first, the most forceful contractions of the palatopharyngeus and the levator palati (either individually or synchronously) were entirely without effect upon the orifice. These experiments demonstrate that no muscle except the tensor palati exerts any influence upon the pharyngeal orifice of the Eustachian tube, and there is no suggestion that the other muscles of the region act as auxiliaries or antagonists to the tensor in its function of opening the tube; for during deglutition there was no variation in the degree of dilatation of the orifice whether the levator palati and palatopharyngeus muscles were severed or were left intact.

The preceding experiments are concerned with the movements of the pharyngeal orifice, and it has been shown that the levator palati plays no part in the regulation of the patency of this portion of the Eustachian tube. It was, however, necessary to try to determine what effect, if any, is exerted by this muscle upon the lumen or isthmus of the canal, to which it is certainly closely related anatomically,

although, as has been pointed out,[24] the muscle does not actually arise from the tube, but is connected with it through an interposed layer of fibrous tissue.

According to one view, it will be remembered, the levator dilates the lumen of the tube by elevating its floor.[19, 24, 25] Another opinion is that the contracting belly of the levator narrows the lumen of the tube by mechanical pressure.[5, 29, 10] Dissections make it appear doubtful that the cartilaginous wall of the tube to which the levator is related can actually be displaced to any extent by the contraction of this muscle. But an attempt was made to study directly the conditions existing within the Eustachian tube during the contraction of the various muscles about it. A manometer was constructed in the following manner: A very small cylindrical balloon, made from very thin sheet rubber, was sealed to a piece of glass tubing bent to suit the direction of the tubal orifice. By means of small-bore rubber tubing, this balloon was placed in communication with a second balloon about the size of an olive, which was situated within an air-tight chamber having a single outlet, from which a second piece of tubing led to the tambour of a delicate compound lever. By means of a

FIG. 1.—Kymographic record. Manometer downward deflections indicate widening of tubal lumen. X = Stimulation of tensor palati. o = Stimulation of levator palati.

T-tube and a stop-cock between the terminal balloon and the encased balloon, both could be inflated to the desired extent; while a second T-tube and stop-cock between the balloon chamber and the tambour, when open, allowed air to be introduced into the first portion of the system without any displacement of the lever; after which it could be closed so that then any displacement of air, however slight, from the little cylindrical balloon, would in turn cause a displacement of air from the chamber into the tambour with a consequent deflection of the sensitive lever. The little terminal balloon, after inflation, was introduced into the Eustachian tube. This was accompanied, of course, by some displacement of air from the balloon, as the walls of the tube tended to close down upon it. Care was taken to see that the pharyngeal orifice was occupied by the glass tube, and that the balloon was allowed to lie entirely within the Eustachian tube, thus eliminating any effect of the movements of the ostium. The hope was that when the various muscles were now stimulated, any change occurring in the size of the lumen would cause air either to pass into or to be driven out of the terminal balloon, and that such a change would be recorded by the lever. The chief difficulty in such an experiment lies in the fact that the introduction of air necessary to inflate the balloon causes sufficient pressure to distend the tube mechanically; and many attempts were made with different degrees of inflation before any trustworthy results could be obtained. In several experiments, however, it was found possible to obtain kymographic tracings in which downward deflections of the lever indicate distinctly a widening of the tubal lumen during contractions of the tensor palati (Fig. 1); nor was there any variation in the extent of the excursion of the lever, whether the levator palati and palatopharyngeus muscles were cut or intact, at rest or contracting simultaneously with the tensor. Stimulation of these latter muscles, and also of the internal pterygoid and superior constrictor of the pharynx, while the tensor palati was at rest, caused not the slightest deflection of the lever in any experiment.

It has been noted by otologists,[5, 12] that a catheter introduced into the Eustachian tube rotates somewhat during deglutition. This movement has been believed to be caused by the change in the shape and caliber of the lumen resulting from muscular action upon the tube, especially through the effect of the levator palati.[5] The phenomenon was here utilized in the attempt to corroborate the manometer experiments. A long, very light straw with a base several millimeters in diameter was introduced into the tube through the pharyngeal orifice. The length of the straw exaggerated the movements of the end within the tube sufficiently to permit satisfactory kymographic tracings to be obtained from the free end. On stimulation of the tensor palati muscle there occurred a marked deflection of the straw. When the internal pterygoid, the levator palati or the palatopharyngeus muscles were stimulated, the straw remained absolutely at rest. Certainly, if the levator palati had caused any change in the caliber of the lumen or position of the walls of the tube (if, for example, the floor had been vigorously elevated as has been assumed[19, 25]), the straw would have suffered some displacement.

These experiments lead us to the conclusion that the tensor palati muscle alone is responsible for any change that may occur physiologically in the patency of the pharyngeal orifice or lumen of the Eustachian tube. This conclusion was supported by nasopharyngoscopic observations made upon a patient in a ward of The Johns Hopkins Hospital. This man had suffered from a unilateral paralysis of the tensor palati muscle following disease of the fifth nerve. The pharyngeal orifice of the tube on the affected side appeared somewhat more patulous than that of the normal side; and during deglutition, the unaffected tube gaped normally, while the orifice on the side of the tensor paralysis remained quite stationary, although the levator palati, palatopharyngeus and superior constrictor muscles were contracting vigorously.

CONCLUSIONS

1. Normally, the Eustachian tubes are closed. They are opened during the swallowing, yawning and sneezing reflexes. They exhibit no independent reflex dilatations either periodic or irregular. Normally, they are not opened by respiratory movements, either quiet or forced, and are unaffected by mouth-breathing or by simple elevation of the soft palate (produced by contraction of the levatores palati alone).

2. Although a most important function of the Eustachian tube is that of equalizing the atmospheric pressure on both sides of the tympanic membrane, the mere existence of a disturbed pressure equilibrium will bring about no regulatory reflex dilatation of the tube, either independently or through the swallowing reflex. Deglutition, as a means of restoring pressure-equilibrium to the ear-drum, is performed, when necessary, consciously or through habit; but this reflex is never set in motion directly by the stimuli arising from tension of the tympanic membrane.

3. The levator palati, the palatopharyngeus, the internal pterygoid and the superior constrictor muscle of the pharynx (each of which has been variously described as a dilator or constrictor muscle of the Eustachian tube), were found to exert, by their contractions, no influence whatever upon the patency of the orifice or lumen of the tube.

4. The tensor palati is the only muscle which is functionally related to the Eustachian tube. Contraction of this muscle is always accompanied by a dilatation of the tubal orifice and lumen. There exists no constrictor muscle of the tube. Relaxation of the tensor palati is followed by a passive return of the tubal walls to the condition of approximation which they normally occupy when at rest.

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HEREDITARY SPASTIC PARAPLEGIA

By V. R. MASON and W. F. RIENHOFF, JR.

(From the Medical Clinic, The Johns Hopkins Hospital)

The four cases of hereditary spastic paraplegia which form the basis of this report are of interest chiefly as examples of a rare hereditary alteration of the central nervous system which has affected members of one family for three generations. The cases differ in minor details from others that have been reported, but in general may be considered as fairly typical instances of the disease.

CASE 1.—Mary Rexroth. Although this woman was not examined by us, a fairly satisfactory description of her symptoms was obtained from members of her family.

She was married at an early age to a healthy man and gave birth to five children, all by easy labor. Two of the children (Case 2 and Case 3) are afflicted with a malady which they believe is similar to that from which their mother suffered. As far back as the informants can recall, her voice was shaky and tremulous, making speech almost unintelligible. She also had a coarse tremor of the arms and hands, which prevented writing and made the use of table utensils very difficult. Her legs were stiff and she dragged her toes while walking. These symptoms grew gradually more pronounced until she became, in later life, practically bedridden. Intelligence was unimpaired and there were no sphincter disturbances. She died at the age of 75 of heart disease.

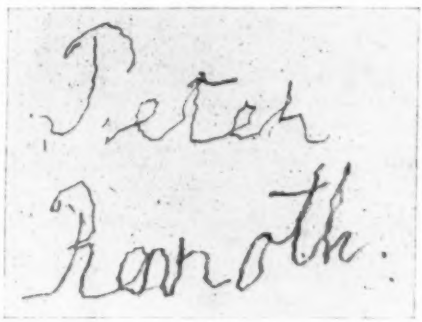

FIG. 1.—Handwriting of Case 2.

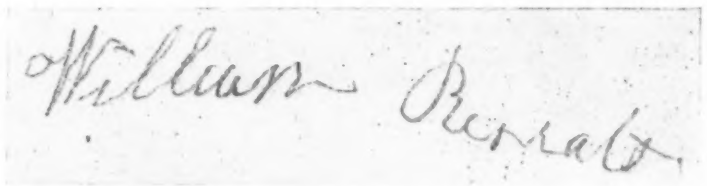

FIG. 2.—Handwriting of Case 3.

CASE 2.—Peter Rexroth. This patient is the son of Mary (Case 1) and a brother of William (Case 3). Aged 61, machinist. He married at the age of 19 years. Of his children one daughter is affected with the same malady (Case 4) and one son is mentally inferior and incorrigible.

Present Illness.—At about the age of 14 patient noticed that he could not run as fast as other boys. Soon afterward tremors of the hands made writing difficult and his voice became tremulous as a result of the "jerking" of his lips when speaking. This was followed by stiffness of the legs and dragging of the feet. The symptoms have gradually become intensified and now it is only with difficulty that he can walk alone.

S. P.—The patient is well developed and well nourished. He is mentally alert and answers questions intelligently.

The pupils are equal, regular, and active to light and on accommodation. There are slight nystagmoid jerkings of the bulbs on lateral deviation; otherwise the extra-ocular movements are normal. Ophthalmoscopic examination shows the fundi to be normal.

The hearing is acute. The tongue is protruded in the mid-line, but is tremulous. On speaking there is a coarse tremor of the tongue and jaw which produces staccato, mouthy speech.

All of the muscles of the trunk and extremities stand out prominently and resist pressure. The legs and, to a less extent, the arms are spastic. There are a few coarse fascicular twitches of the muscles. Muscle strength is fair in the arms, diminished in the legs. There is a continuous coarse tremor of the hands and arms which becomes much more marked on volitional effort (Fig. 1). There is also a coarse tremor of the lower extremities, only, however, when purposeful movements are attempted.

Sensation is intact. The sphincters function normally. The tendon reflexes are exaggerated, especially in the lower extremities. There is a marked jaw-jerk. No clonus. Bilateral Babinski phenomenon. Abdominal reflexes present. The gait is typically spasto-paretic with a tendency toward a scissor-gait. There is slight bilateral pes equino-varus. The patient shows no ataxia, dysdiadokokinesis, or disturbances in knee-heel and finger-nose tests, except those dependent upon intention tremors.

Laboratory Examinations.—B. P. 125/75. R. B. C. 4,408,000. W. B. C. 8360. Hgb. 60 (Sahli). Differential P. M. N. 72 per cent; S. M. 20 per cent.

The blood Wassermann test negative. Phthalein excretion 55 per cent in two hours.

C. S. F.: Normal pressure. One cell per c. mm. Globulin not present. Wassermann test negative. Gold sol curve negative.

X-Ray: Spine, slight arthritis. Gastro-intestinal tract, negative. Stool negative. Urine not remarkable.

Summary.—Spastic paraplegia, with coarse tremor of arms and hands, markedly accentuated by intentional movements. There is staccato speech dependent upon spontaneous and intention tremor of the jaw and tongue.

CASE 3.—William Rexroth. This patient is also a son of Mary (Case 1) and a brother of Peter (Case 2). Aged 68; barber.

He first began to notice stiffness and weakness of the legs at the age of 14, and soon afterward tremors of the hands and jaw.

S. P.—The patient is of normal intelligence and well developed physically. The pupils are active, the fundi and the extra-ocular movements are normal. There are tremors of the jaw and tongue, very marked during speech, and producing a jerky, staccato intonation. There is also a coarse, irregular tremor of the hands and arms, accentuated by purposeful movements (Fig. 2), but also present during rest.

The tendon reflexes of the arms, and more especially of the legs, are hyperactive. No clonus. Plantar response is normal. Abdominal reflexes present.

The gait is spasto-paretic, but there is no ataxia. Some loss of power of the legs can be demonstrated.

Sensation is intact. No sphincter disturbances.

Summary.—Spastic paraplegia with intention tremor of jaw, tongue, and arms.

Case 4.—Margaret Rexroth, aged 26. Daughter of Peter (Case 2).

The birth was normal, the labor easy; the mother is perfectly healthy. The patient learned to walk at the age of two. At 4 years of age she began to drag the right foot slightly. She started to school at the age of 7 but at 14 had reached only the second grade. During this period her speech became affected and she tripped and fell frequently. In 1914 she could walk with assistance but the gait was very stiff and unsteady.

S. P.—November, 1914 (patient aged 20). The patient is well developed. The mentality is impaired. The Binet-Simon age is 9 years. The cranial nerves function normally. Fundi normal. Speech is disturbed, due to mouthing of words. There is a constant coarse tremor of the hands and arms. Tendon reflexes are all exaggerated. Patellar and ankle clonus can be elicited. The plantar response is equivocal.

Exmination in February, 1920. All of the symptoms have progressed since the above recorded examination. A remarkable coarse, jerky tremor of the hands, arms, jaw and tongue is constantly present and markedly accentuated by purposeful movements. Speech staccato and difficult to understand. *Third riding artillery brigade* is repeated. "*Third riling tullary bade*"; *Methodist Episcopal*, "*Mest piscal.*" The legs are very spastic. The tendon reflexes are all exaggerated, especially in the lower extremities. There is a patellar and an ankle clonus on each side. The Babinski phenomenon is equivocal.

The patient is now unable to walk and there is marked disuse atrophy of the leg muscles. The sphincter muscles function normally and sensation is not impaired.

Summary.—Spastic paraplegia. Mental inferiority. Intention tremor of arms. Speech disturbance.

Strümpell,[1] in 1880, reported two cases of hereditary spastic paraplegia, and although at the time he was not certain of the exact nosology of the symptom-complex, he had an opportunity a few years later to examine the central nervous system of one of his patients and to demonstrate the pathological basis of the syndrome. Since then the records of about sixty affected families have appeared in the literature and are summarized by Lorrain[2] Deléarde and Minet,[3] Bono,[4] and Rhein.[5]

Usually, the malady affects individuals in only one generation but in seven of the families recorded characteristic symptoms of the disease were present in more than two generations. Our own cases offer still further proof of the true hereditary character of this type of degeneration of the central nervous system.

Etiological factors, other than heredity, are not known. In a few instances, however, there was consanguinity and in others the parents of the patient were either feeble-minded or presented certain anomalies of development or signs of degeneracy. The relation of these factors to the hereditary occurrence of degeneration of the central nervous system is not understood fully at the present time. A critical summary of the subject will be found in a recent article by Jendrassik.[6]

The age at which symptoms of the affection first appear is not constant. Strümpell[7] stated that there was a juvenile form beginning at about puberty, and an adult form which usually appears during the fifth or sixth decade. Since the time of his report cases have also been observed in infancy and early childhood. It is therefore apparent that symptoms of the disease may become manifest at any age, although it is characteristic of hereditary diseases of the central nervous system that the age of onset is about the same in individuals of the same generation.

So far as the reported cases show, there is no evidence that sex plays any important rôle, either in the occurrence or in the transmission of the disease. The cases herein recorded are divided equally as to sex; moreover, the disease was transmitted once by an affected female and once through an unaffected female.

The fundamental symptom, from which the disease derives its name, is a spastic paraparesis which may involve the upper extremities to some extent after the condition has progressed for many years. Upon this basic symptom one or more of an array of subsidiary symptoms are usually engrafted. The most important of these are tremor of the tongue, as a rule intentional in type, disturbances of speech, optic atrophy, nystagmus, ocular palsies, bulbar disturbances, scoliosis, pes equino-varus, ataxia, muscular atrophies, and occasionally some mental impairment. Sensation is usually unaffected, as are also the sphincter functions.

It is not possible to group the reported cases into rigid clinical types on account of the variety of syndromes which have occurred from combinations of the symptoms enumerated above. In a few cases the patients have presented only a spastic paraplegia; in the greater number, however, the symptomatology has approached that commonly observed in hereditary ataxia of the Friedreich or Marie type, and indeed in not a few instances a differential diagnosis has been difficult or impossible. Such cases have been regarded by some neurologists as transition forms between the spastic and the ataxic degenerations of the nervous system—a point of view expressed by Jendrassik and, as we shall see farther on, supported by certain clinical and histological evidence.

In the first place, the etiology of the three diseases is identical and the clinical course essentially the same. They all begin usually about puberty, progress slowly to a certain point and then remain stationary. Moreover, typical or "pure" cases of any of the three affections are rare. This is especially true of Marie's ataxia, in which the symptomatology may resemble Strümpell's paraplegia, on the one hand, or Friedreich's ataxia on the other, and therefore may be considered as a transition form between the spastic and the ataxic types. Furthermore, even in rather typical cases of one of the diseases, symptoms common to all three, such as nystagmus, tremor, or pes equino-varus, have been observed.

Secondly, the pathological anatomy of three affections, although not at present fully understood, is in many respects strikingly similar. As a rule, there is in each disease a well

marked combined sclerosis of the postero-lateral tracts of the cord, of the type characteristic of hereditary degenerations of the nervous system. The extent to which the several tracts are involved, however, varies in the individual cases in accordance with the symptomatology. Thus, in spastic paraplegia the posterior tracts and cerebellar tracts may be only slightly involved, while the pyramidal tracts are markedly affected. In Friedreich's ataxia, on the contrary, the pyramidal tracts may be but slightly altered. The pathological basis of Marie's ataxia is somewhat more complicated. In certain instances only a diminution in size of the cerebellum and cord was observed, while in other cases there was also a well marked sclerosis of cord tracts of the same character as that found in the other hereditary degenerations.

Certain other alterations not characteristic of any of the three maladies have also been observed in many cases. The most important of these are diminution in the number of fibers in the white tracts of the cord and the number of Betz cells and anterior horn cells. In some cases, also, the whole central nervous system has appeared to be unusually small. In general, these changes have been observed as frequently in the spastic as in the ataxic forms of hereditary degeneration.

There is much evidence, therefore, to support the assumption that the hereditary degenerations of the nervous system, characterized by ataxia (Friedreich's ataxia) alone, ataxia and paraplegia (Marie's ataxia), and paraplegia alone (hereditary spastic paraplegia) are all syndromes or clinical forms of the same morbid entity. The definite proof of the validity of this assumption, however, can be adduced only by a more complete correlation of clinical and pathological studies than is possible at the present time.

Diagnosis.—The differential diagnosis from multiple sclerosis is often difficult on account of the similarity of symptomatology; but the familial occurrence of the disease and the absence of remissions is of help in excluding disseminated sclerosis. Furthermore, changes in the cerebrospinal fluid, commonly present in that disease, have not been found in the few cases of hereditary spastic paraplegia in which lumbar puncture has been performed.

Isolated instances of hereditary spastic paraplegia probably occur. The diagnosis of such cases in the absence of a familial or hereditary history would be doubtful at best. Moreover, it would be necessary to exclude the commoner causes of spastic paraplegia.

From Friedreich's or Marie's ataxias differential diagnosis is largely of academic interest. In some instances it is impossible, but in the majority, if the presence or absence of spastic paraplegia or ataxia is employed as the basis of differentiation, it is possible to place the disease in its proper group. There will always, however, be some cases which are best classified as transition forms.

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